Pathology of Peripheral Neuroblastic Tumors in Children: Neuroblastoma and its Biological Spectrum. An Update Based on the Upcoming ***WHO PAED5***

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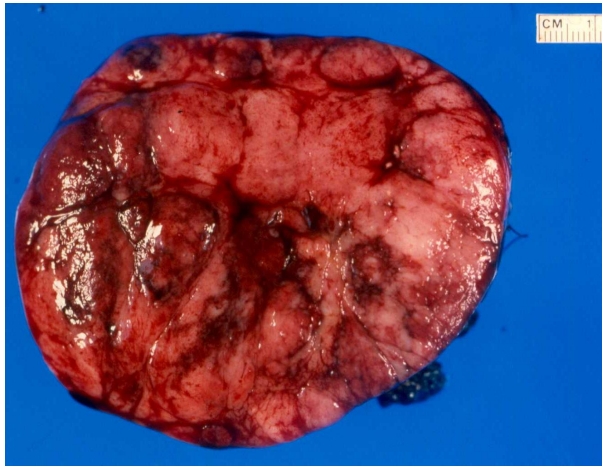
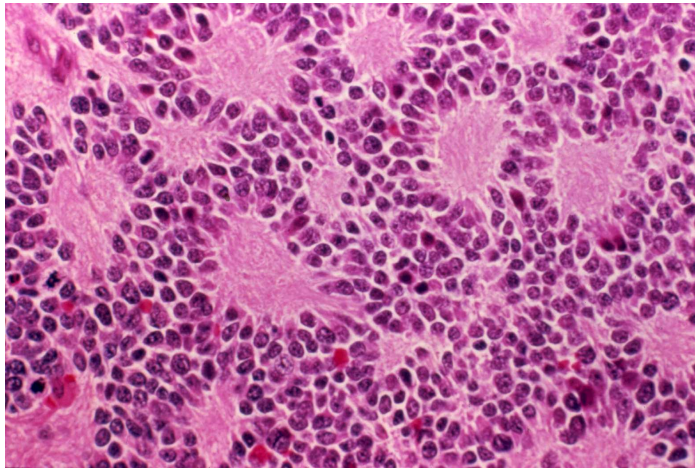




Homer Wright rosettes. Courtesy of J. Carrillo-Farga

@mreyesm

IX Jornada Educación Médica Continua 2021
Sociedad Chilena de Anatomía Patológica
29 de septiembre de 2021

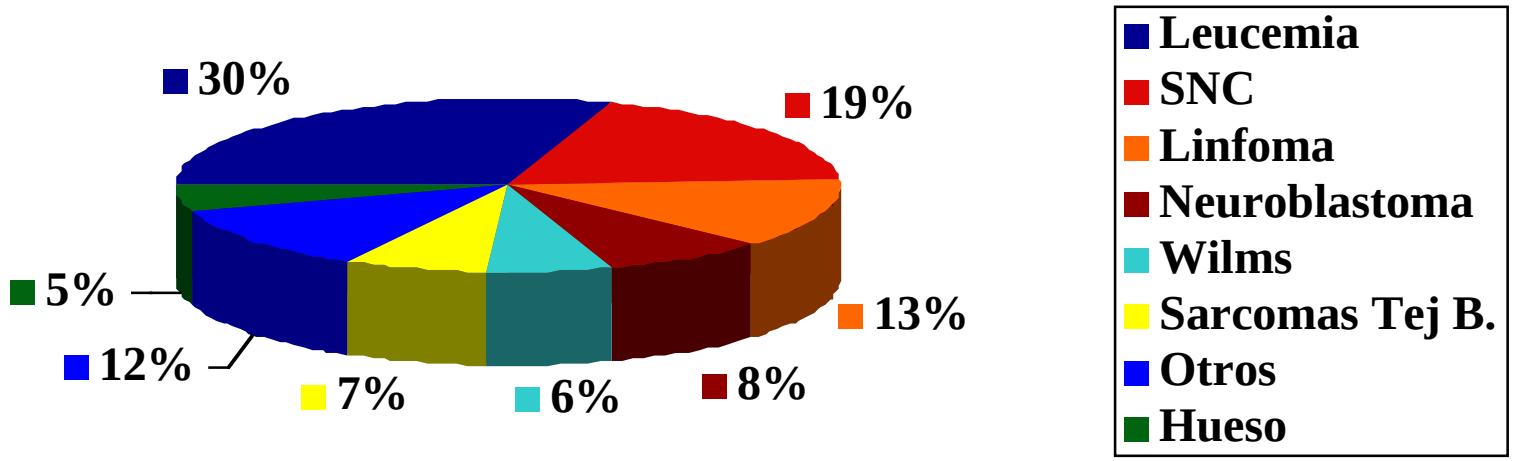
Outline

- Development is the key.
- Cancer in children.
- The neural crest and its derivatives→ neurocristopathies.
- Peripheral neuroblastic tumors in children. Pathology and salient biological features.

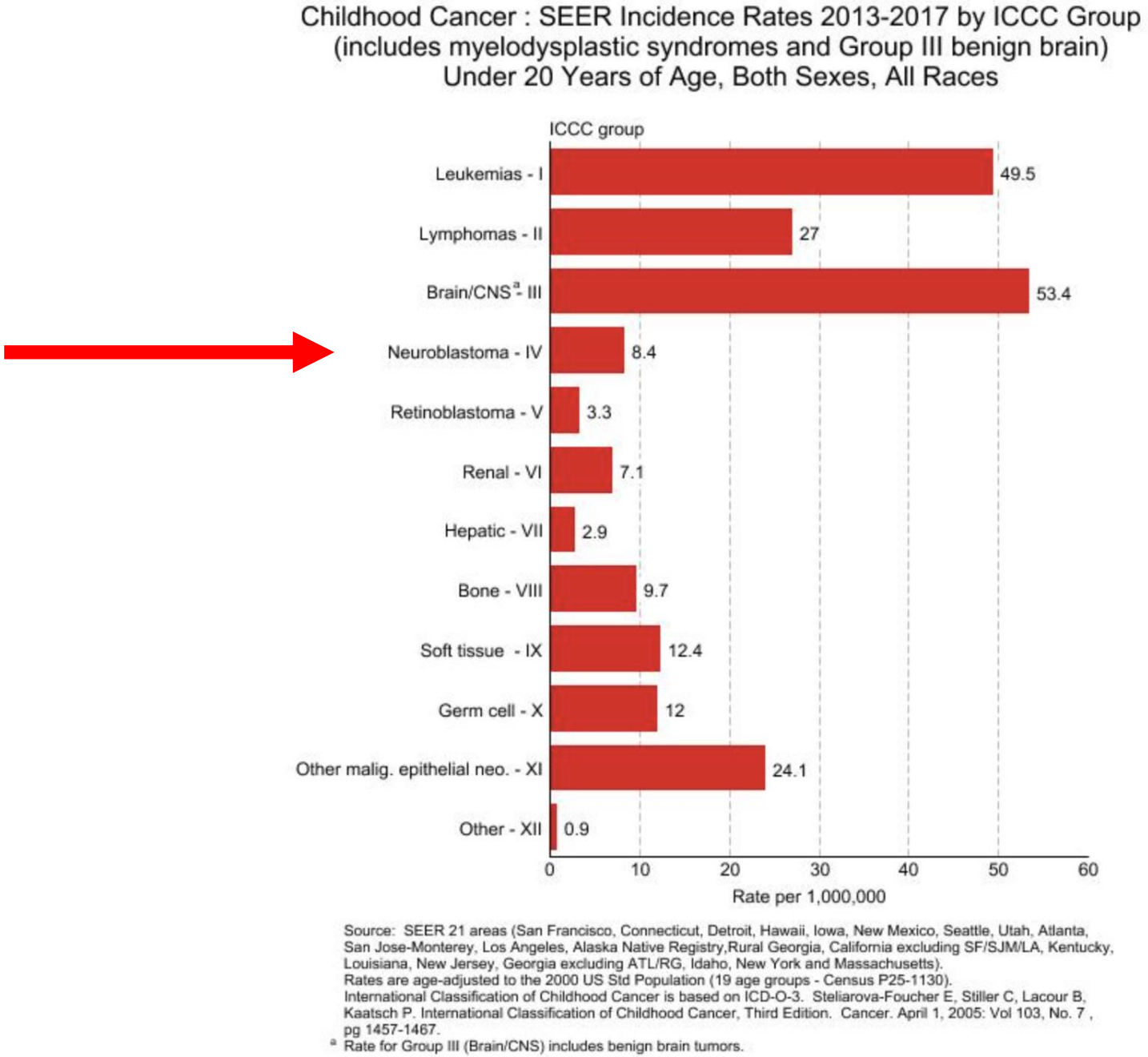
Development is the key

- The pediatric patient is an organism in development and as such, in Pediatric Pathology we need to incorporate the developmental angle if we want to understand diseases of children.
- This is especially true in all lesions derived from the neural crests.
- The spectrum of Neuroblastic Tumors is the best example of this need.

Cancer in children up to15 years of age



Pizzo & Poplack, 1993



https://seer.cancer.gov/csr/1975_2017/browse_csr.php?sectionSEL=29&pageSEL=sect_29_zfig.01

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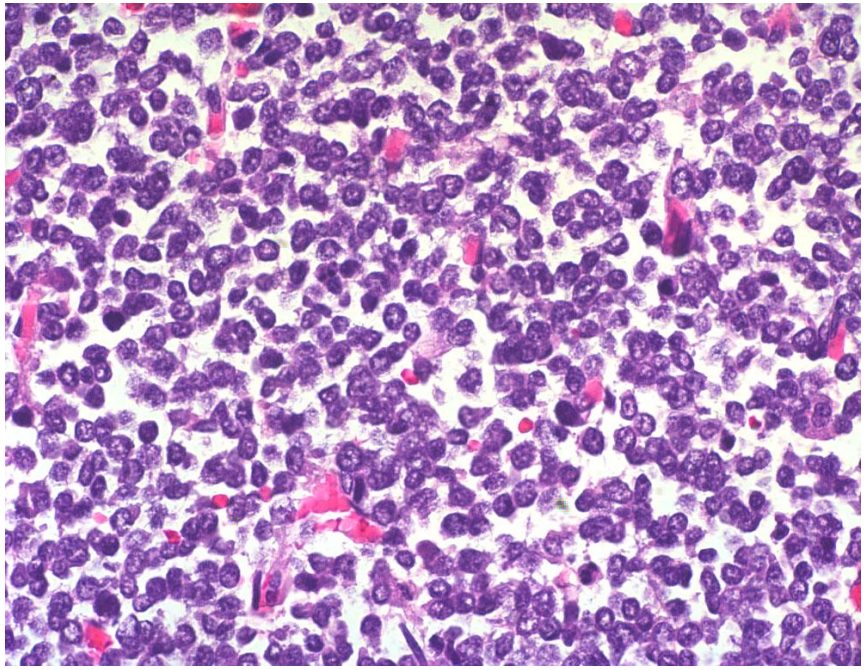
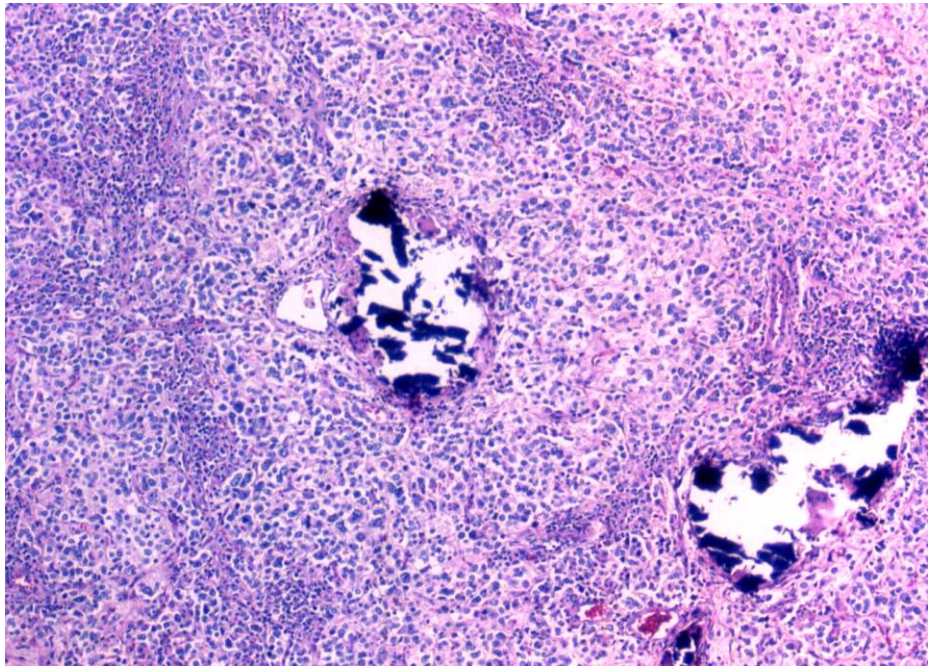
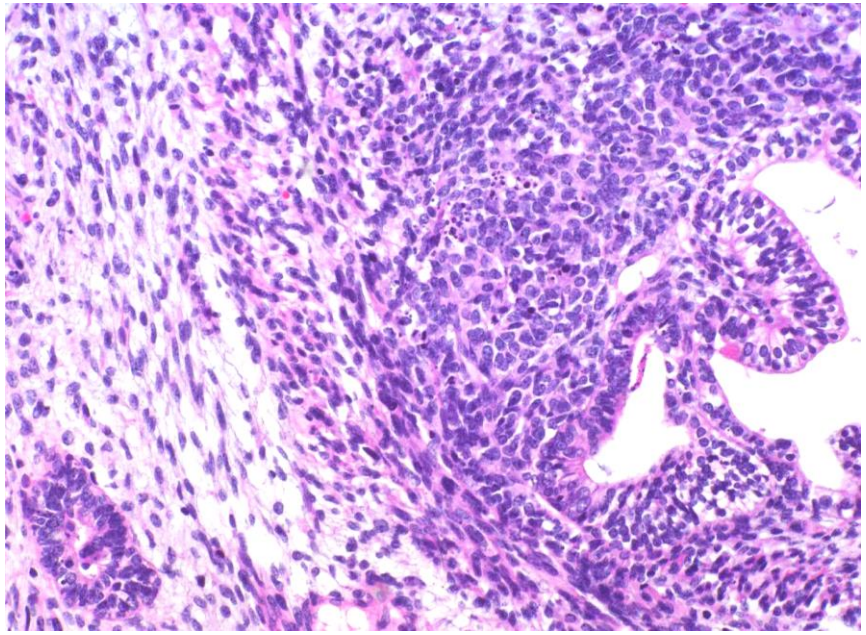
Lymphoma

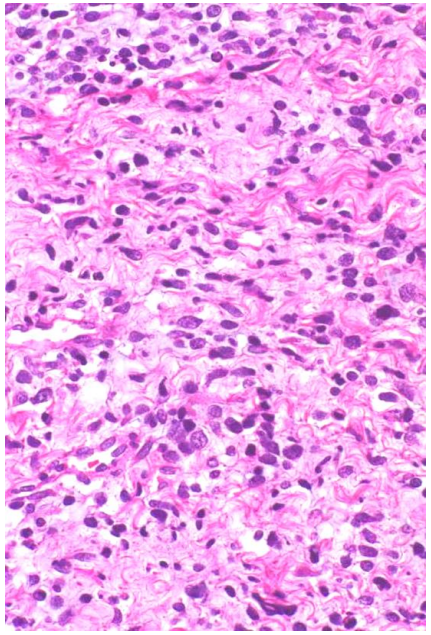


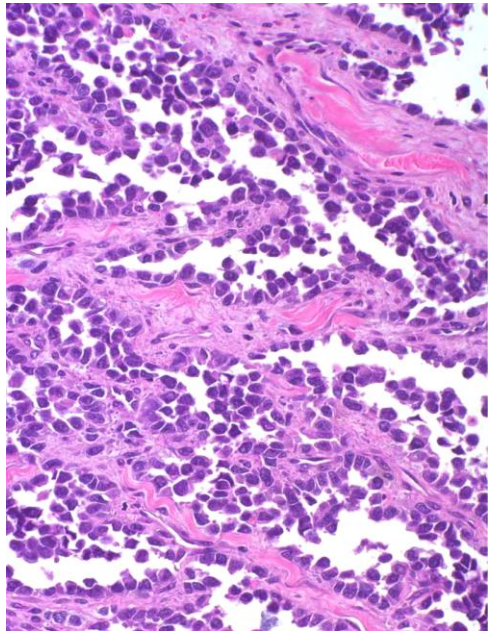


Neuroblastoma

Wilms tumor
(nephroblastoma)







Rhabdomyosarcoma

“The only interesting thing about vertebrates is the neural crest”

Quoted in Thorogood, 1989, Trend Neurosci 12:38

The Neural Crests represent multiple caravans of migrants leading to melanization, peripheral innervation, cardiac septation and many other functions.

Miguel Reyes-Múgica

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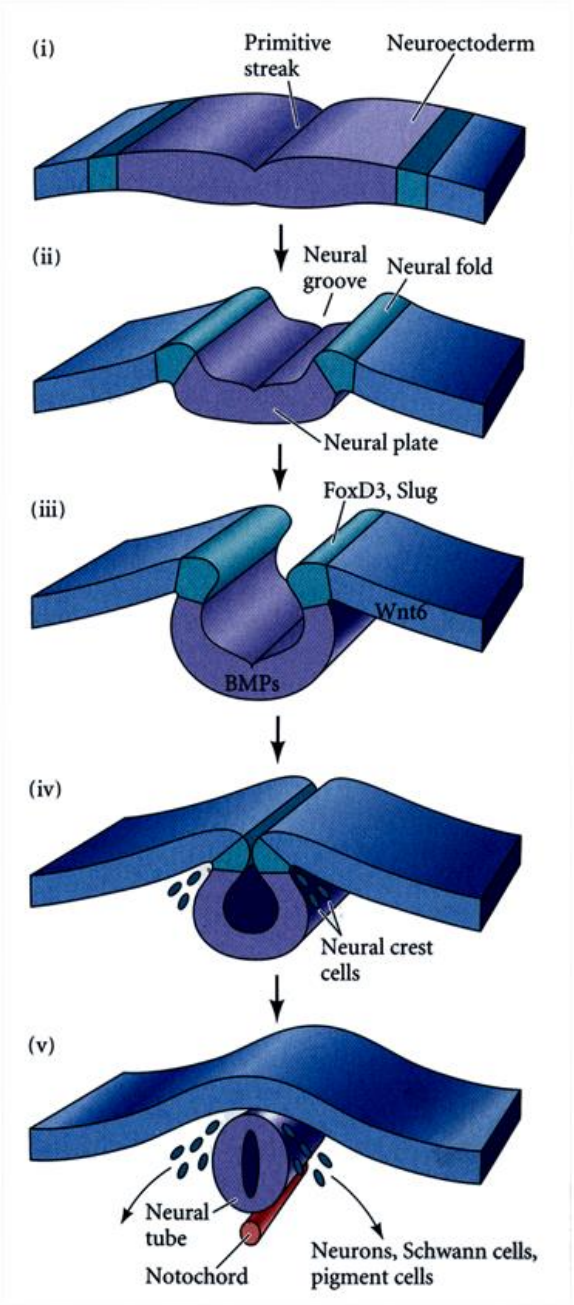
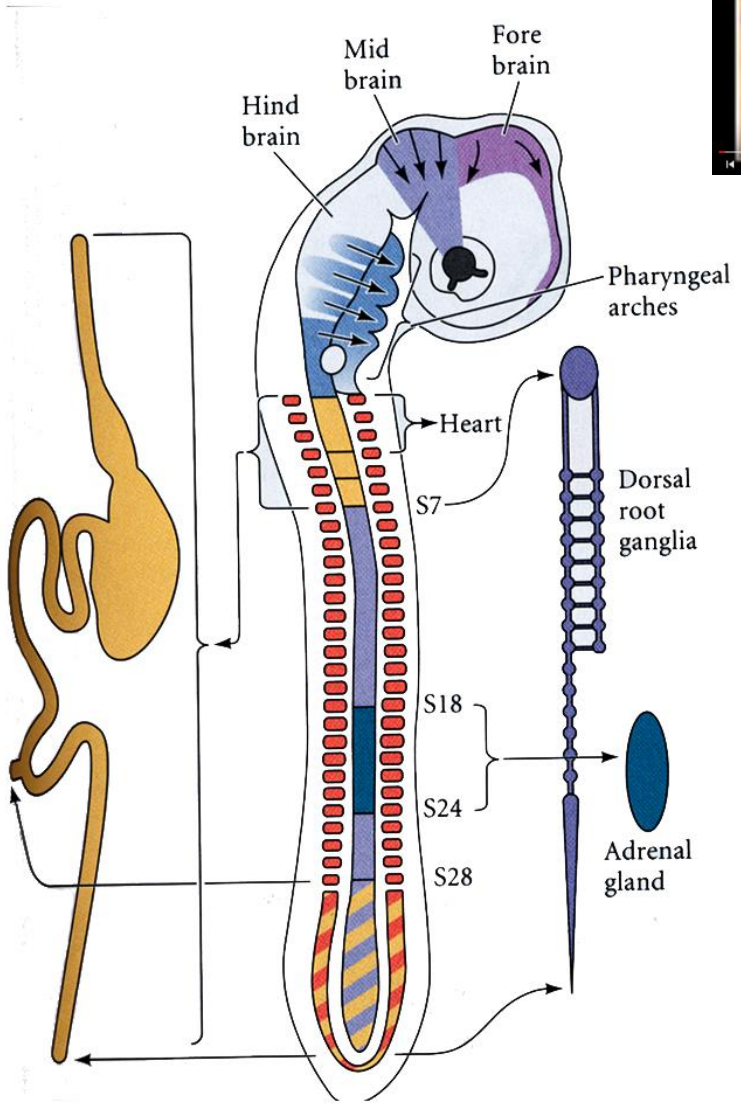
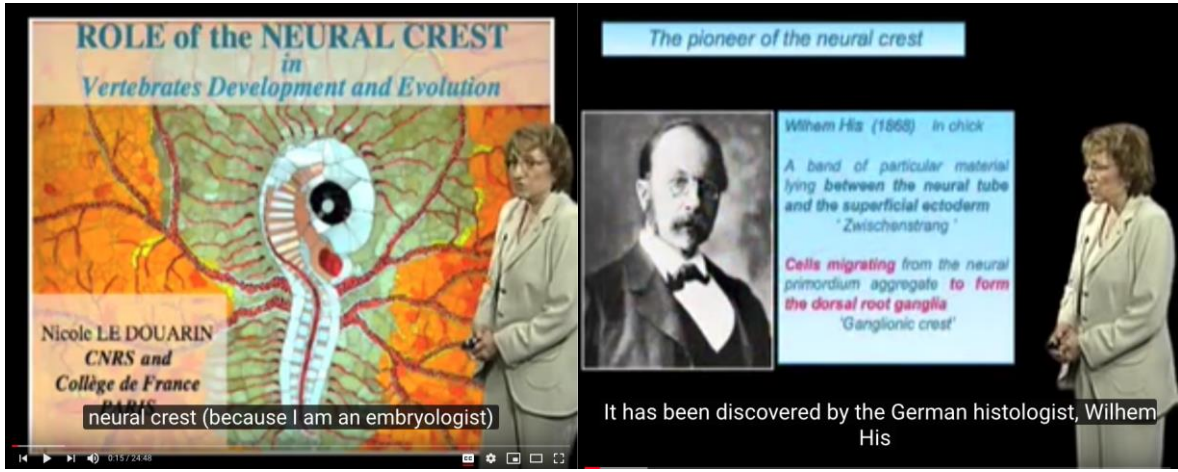


Neural Crest Cells and Axonal Specificity
Gilbert & Barresi. Developmental Biology, 2006, 2016

Neural crest domains:

- Cephalic
- Trunk
- Vagal & Sacral
- Cardiac





https://youtu.be/Our-x4WS4JI

https://youtu.be/Our-x4WS4JI

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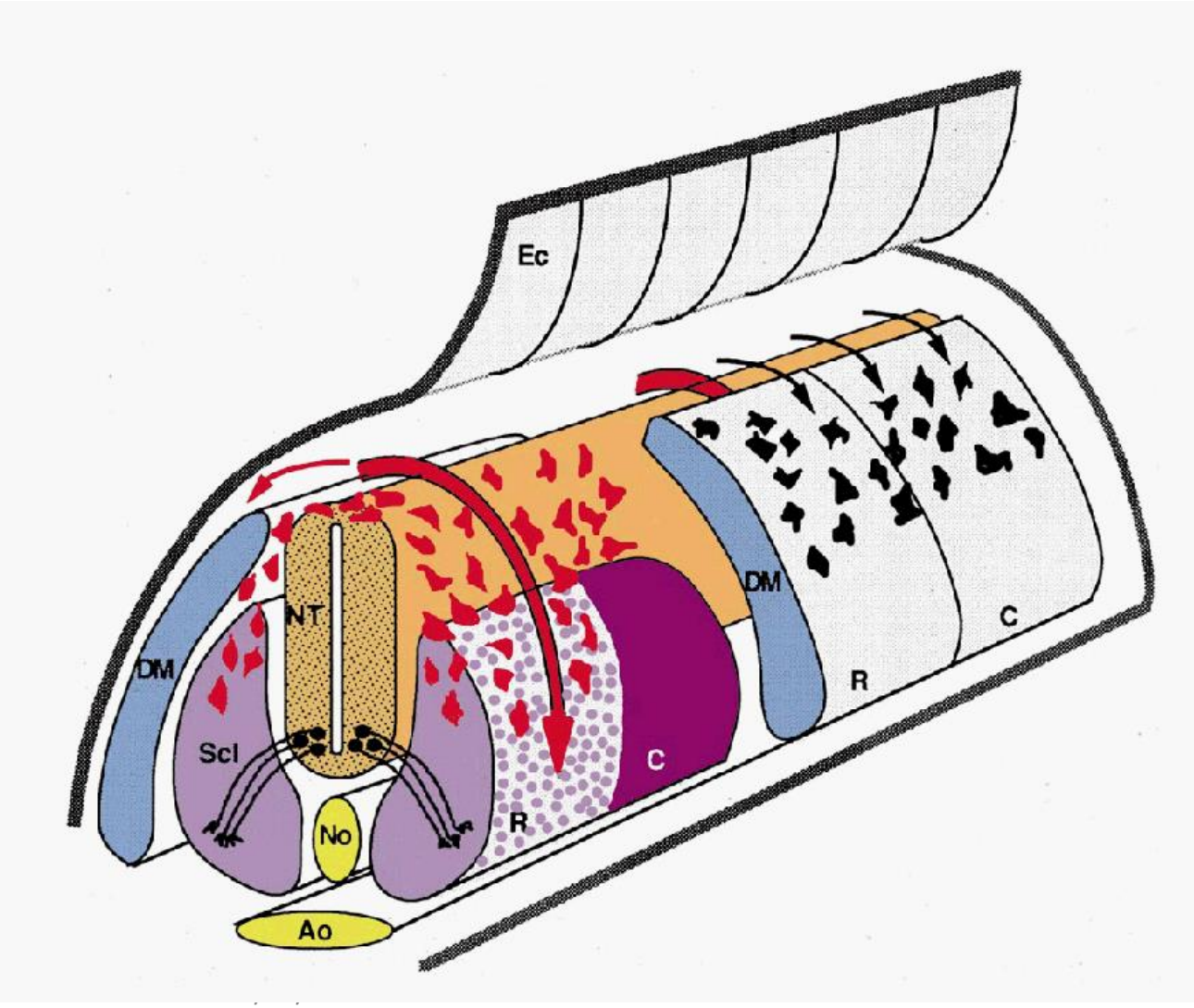
Trunk-level neural crest derivatives

- **Entire peripheral nervous system**
  - glia
  - neurons
  - sheath/support
    - Melanocytes
- Certain endocrine cells
  - **adrenal medulla**
  - calcitonin-secreting

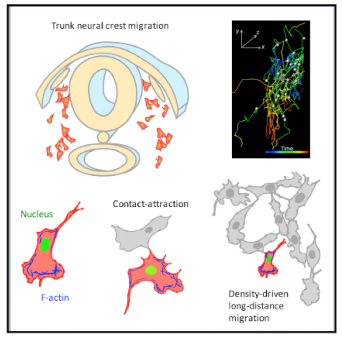


Cell Reports

Article

In Vivo Quantitative Imaging Provides Insights into Trunk Neural Crest Migration

Graphical Abstract



Authors

Yuwei Li, Felipe M. Vieceli, Walter G. Gonzalez, Ang Li, Weiyi Tang, Carlos Lois, Marianne E. Bronner

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mbronner@caltech.edu

In Brief

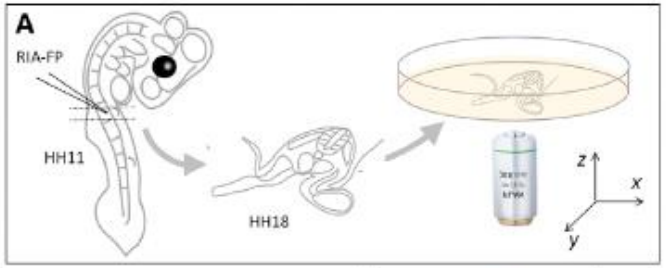
Li et al. combine quantitative imaging with perturbation analysis to define the cellular dynamics driving trunk neural crest migration. Unlike chain migration at other axial levels, trunk neural crest cells move as individuals driven by the combined effect of lamellipodia mediated directionality, together with cell-cell contact and cell density.

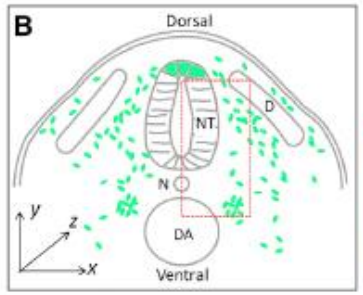
Highlights

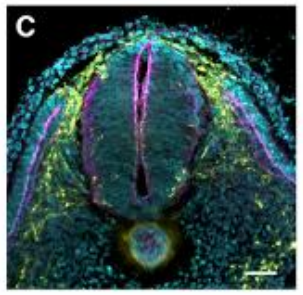
- Trunk neural crest cells migrate individually and undergo a biased random walk
- These cells show multiple types of cell-cell contacts, including contact attraction
- Cell migration and cell-cell contact are actively influenced by mechanical forces
- Manipulating cell density translates individual cell motion into chain migration

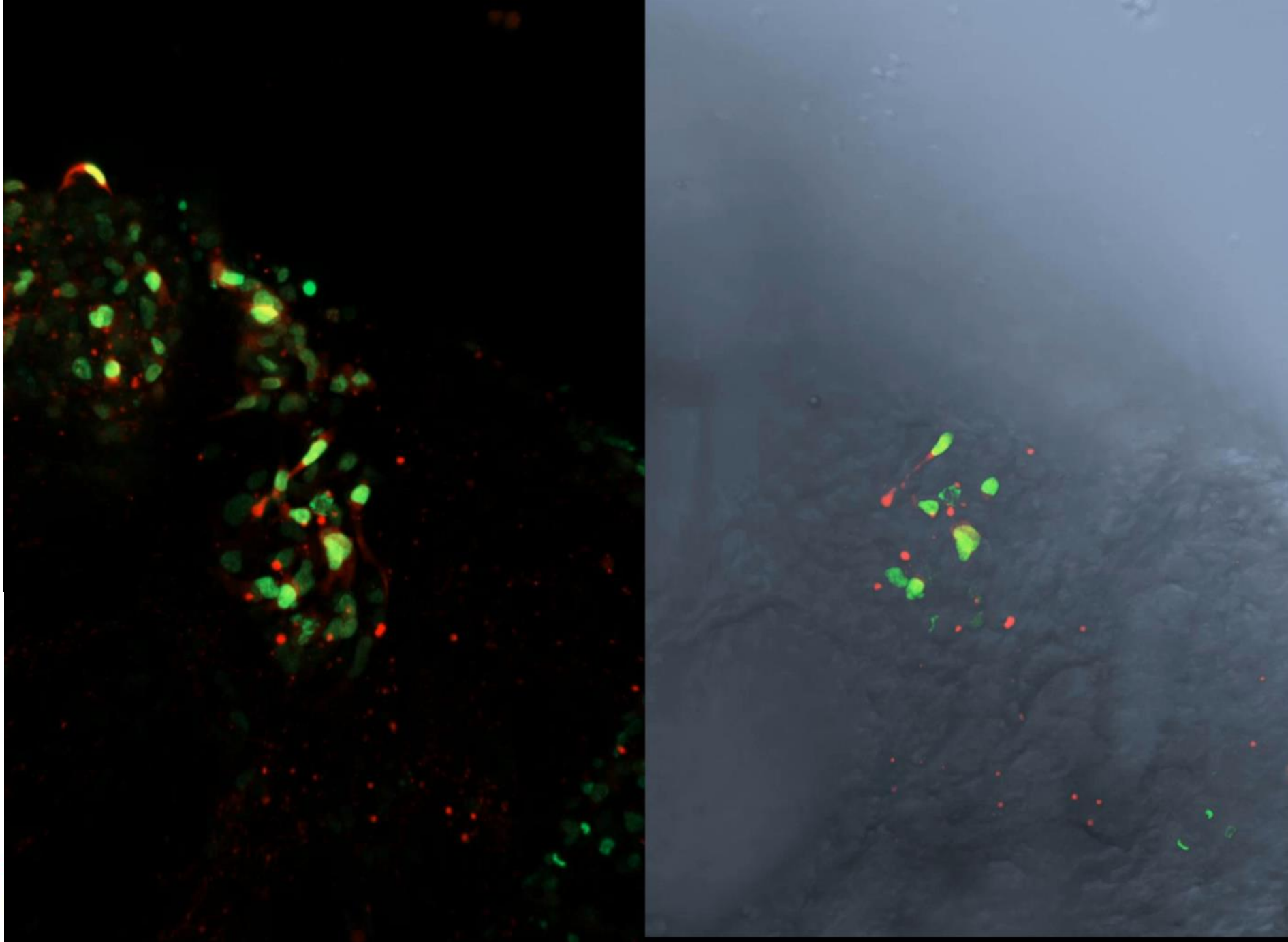
Li et al., 2019, Cell Reports 26, 1489–1500
February 5, 2019
https://doi.org/10.1016/j.celrep.2019.01.039

CellPress









Neurocristopathies

THE NEUROCRISTOPATHIES
A Unifying Concept of Disease
Arising in Neural Crest Maldevelopment
*Robert P. Bolande, M.D.**
HUMAN PATHOLOGY–VOLUME 5, NUMBER 4 *July 1974*

Robert P. Bolande, M.D.
(1926-2006)

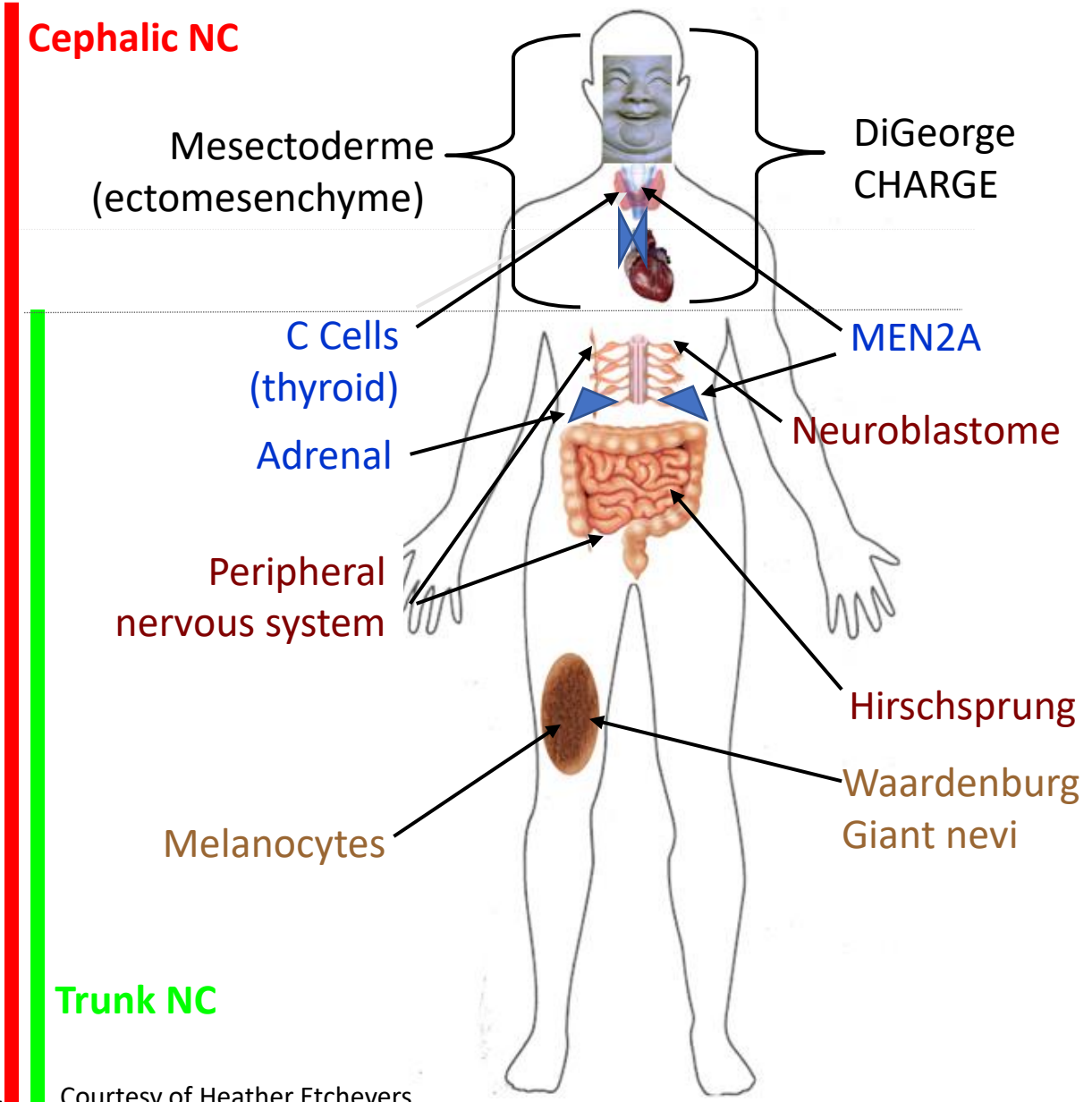
- Simple Neurocristopathies
  - Dysgenetic
    - Hyperpigmentary: **cong. mel. nevi**, lentigo, ephelides, café au lait spots, **neurocutaneous melanosis**
    - Hypopigmentary: albinism, part. alb. (piebaldism)
    - **Hirschsprung, dysganglionoses**
    - Craniofacial mesectodermal malf.: Treacher Collins S., Frontonasal dysp., acrofacial dysost., Pierre Robin S., Facial clefting S., Fetal-alcohol S., retinoic embryopathy
  - Neoplastic: **Neuroblastoma**, Med. Thyroid ca., Pheochromocytoma, Carotid body tumor, Paraganglioma, Retinal anlage tumor, PNET/Ewing Ss., meningiomas
- Complex Neurocristopathies
  - Dysgenetic
    - Waardenburg S.
    - Waardenburg S. & HSCR
    - Piebaldism & HSCR
    - DiGeorge S. and variants
  - Neoplastic
    - von Recklinghausen D.(NF1)
    - MEN2A & 2B
  - Neoplastic and dysgenetic
    - Nbl & HSCR, DiGeorge S. & von Recklinghausen D.
    - Fam. Nbl & HSCR
    - MEN2A & HSCR

Mod. from Bolande, 1974 & 1997

A neurocristopathy is…

Clinical consequences of defects in neural crest cells

- Labiopalatine clefts (1/1000)
- **Cardiac outflow malformations (1/300)**
- Neuroblastoma (10% of pediatric cancers)
- Melanoma, schwannoma, pheochromocytoma …



Etchevers et al. Adv Exp Med Biol. 2006 589:213-34.

Courtesy of Heather Etchevers

Molecular and Cellular Endocrinology 518 (2020) 110998

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Stem cells, evolutionary aspects and pathology of the adrenal medulla: A new developmental paradigm

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ARTICLE INFO

Keywords:
Schwann cell precursors
Chromaffin cells
Oxygen-sensing
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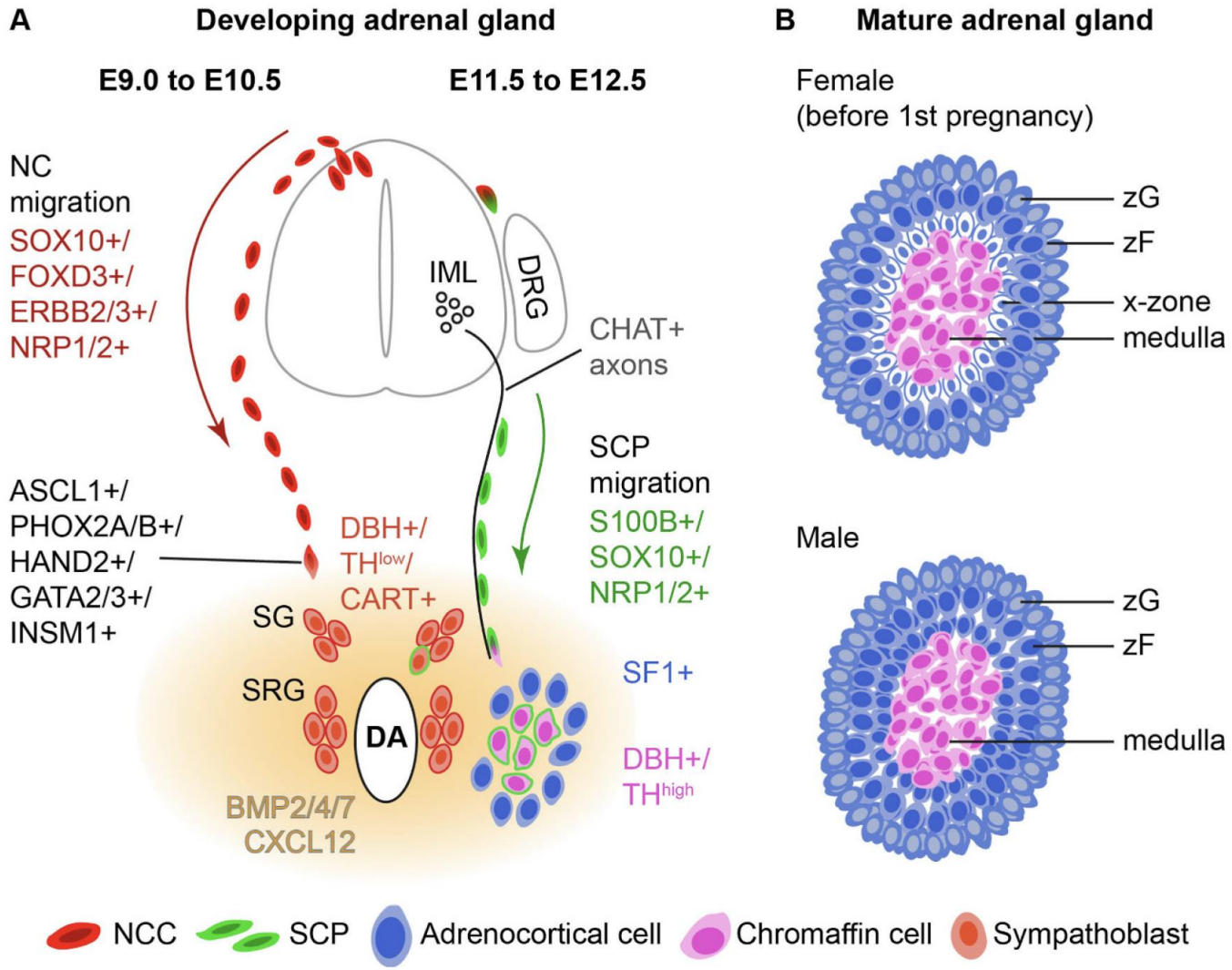
Paraganglioma
Pheochromocytoma

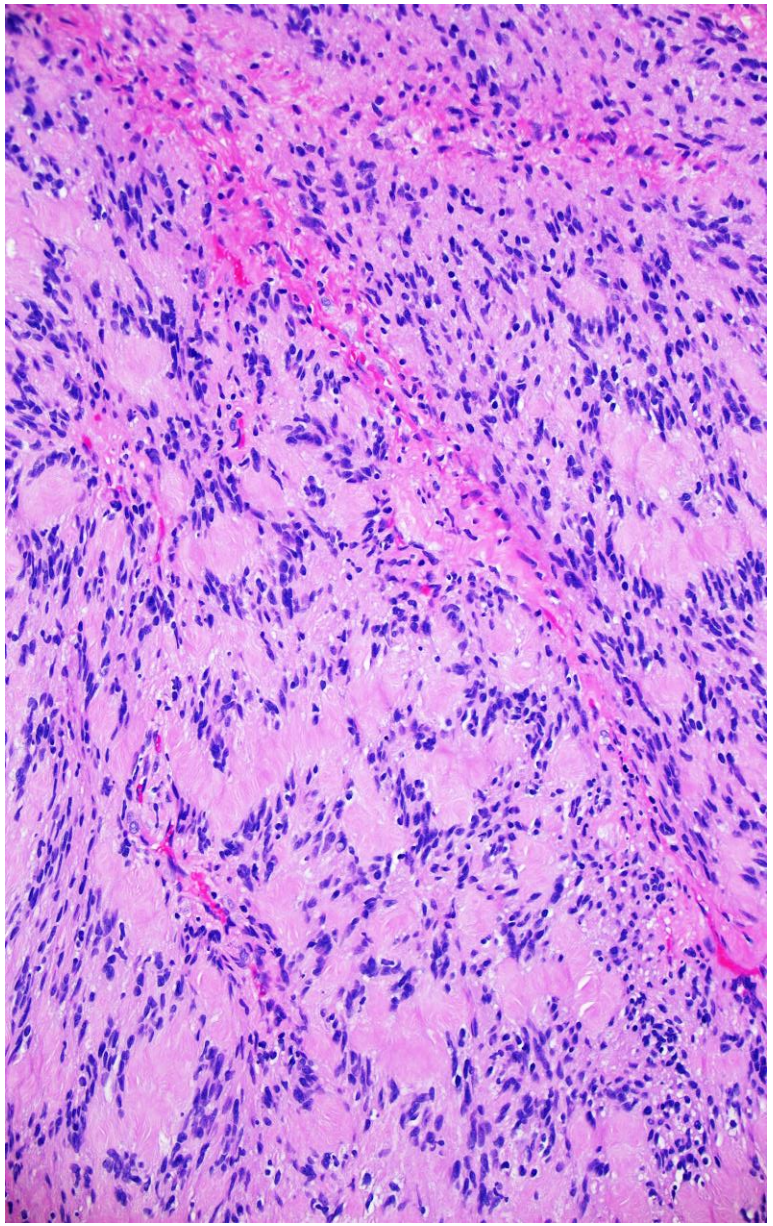
ABSTRACT

The mammalian adrenal gland is composed of two main components; the catecholaminergic neural crest-derived medulla, found in the center of the gland, and the mesoderm-derived cortex producing steroidogenic hormones. The medulla is composed of neuroendocrine chromaffin cells with oxygen-sensing properties and is dependent on tissue interactions with the overlying cortex, both during development and in adulthood. Other relevant organs include the Zuckerkandl organ containing extra-adrenal chromaffin cells, and carotid oxygen-sensing bodies containing glomus cells. Chromaffin and glomus cells reveal a number of important similarities and are derived from the multipotent nerve-associated descendants of the neural crest, or Schwann cell precursors. Abnormalities in complex developmental processes during differentiation of nerve-associated and other progenitors into chromaffin and oxygen-sensing populations may result in different subtypes of paraganglioma, neuroblastoma and pheochromocytoma. Here, we summarize recent findings explaining the development of chromaffin and oxygen-sensing cells, as well as the potential mechanisms driving neuroendocrine tumor initiation.

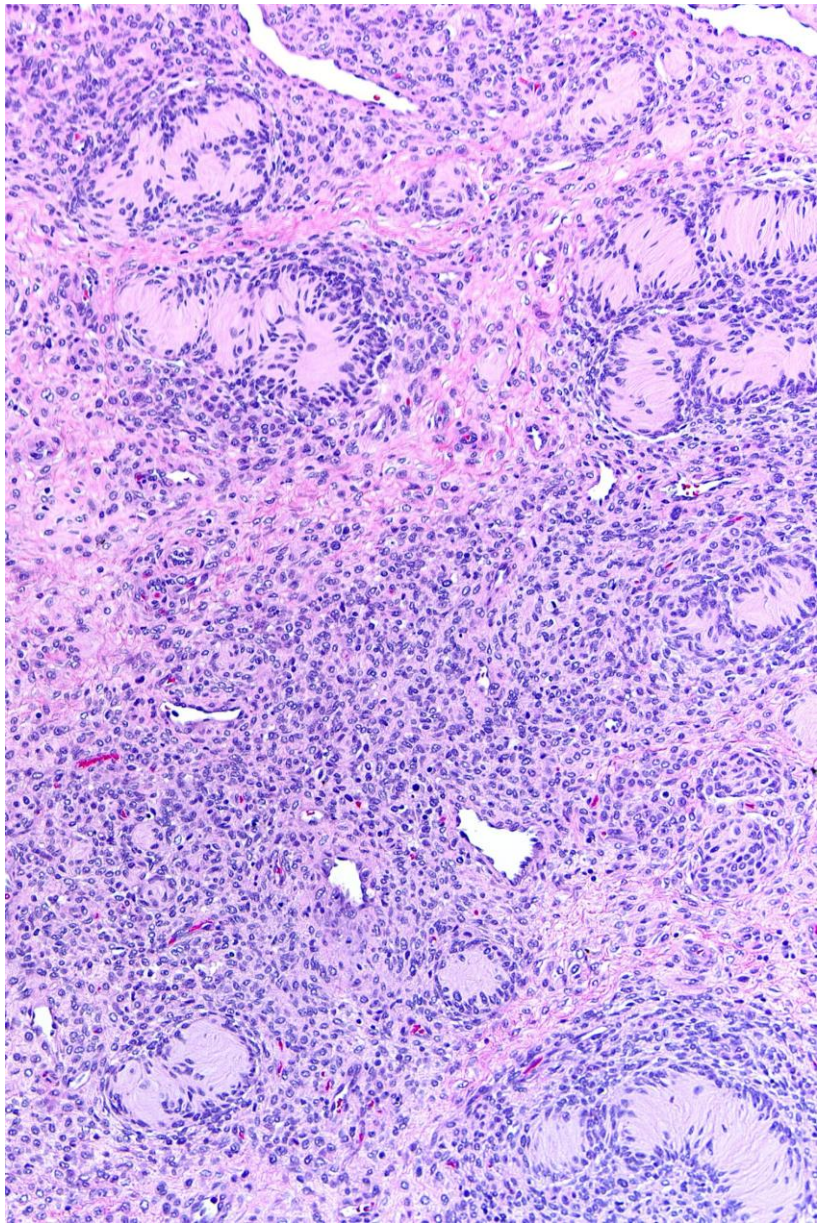
Professor
Chair, Department of Neuroimmunology.
Center for Brain Research)
Medical University of Vienna, Austria



Schwannoma



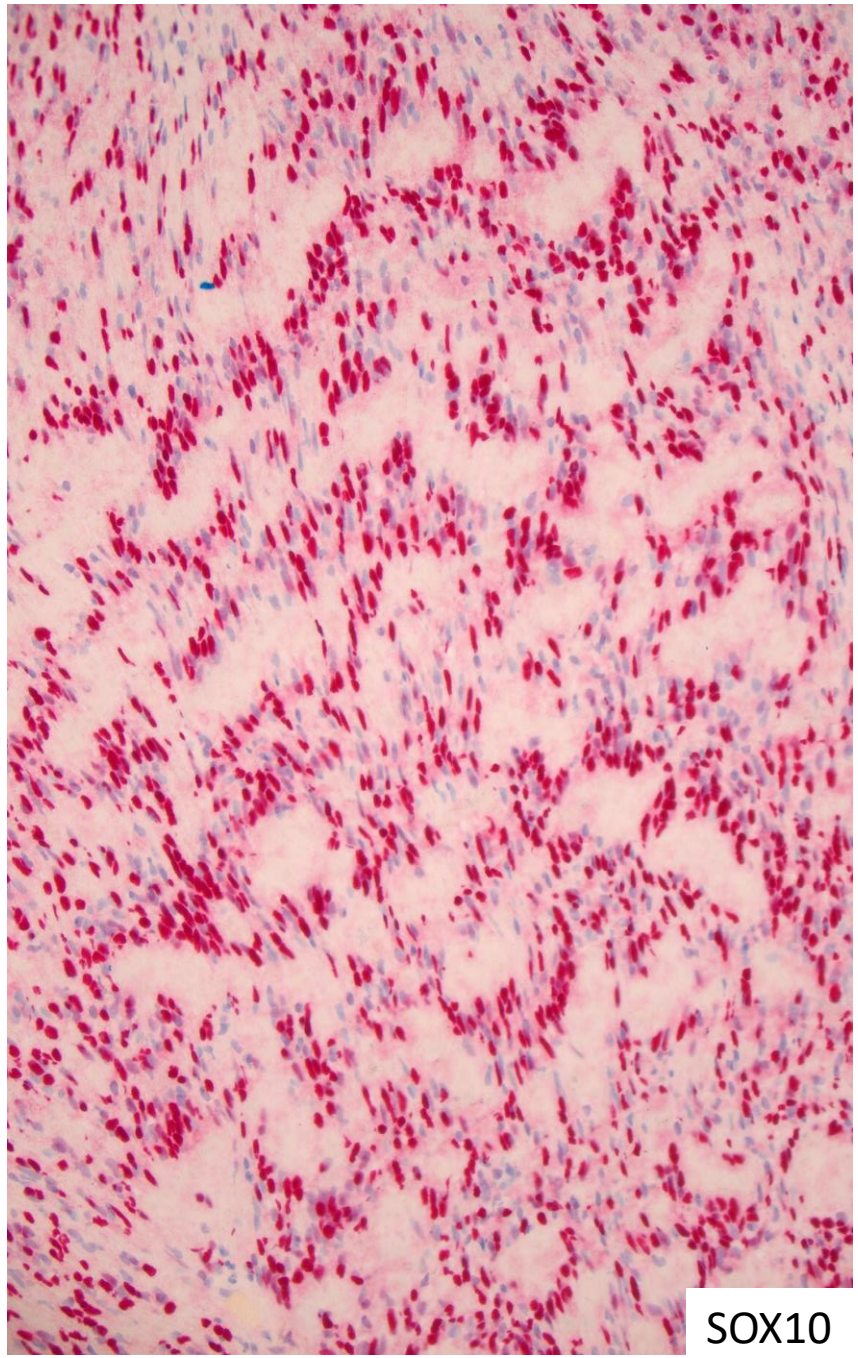
CMN “neurotized”



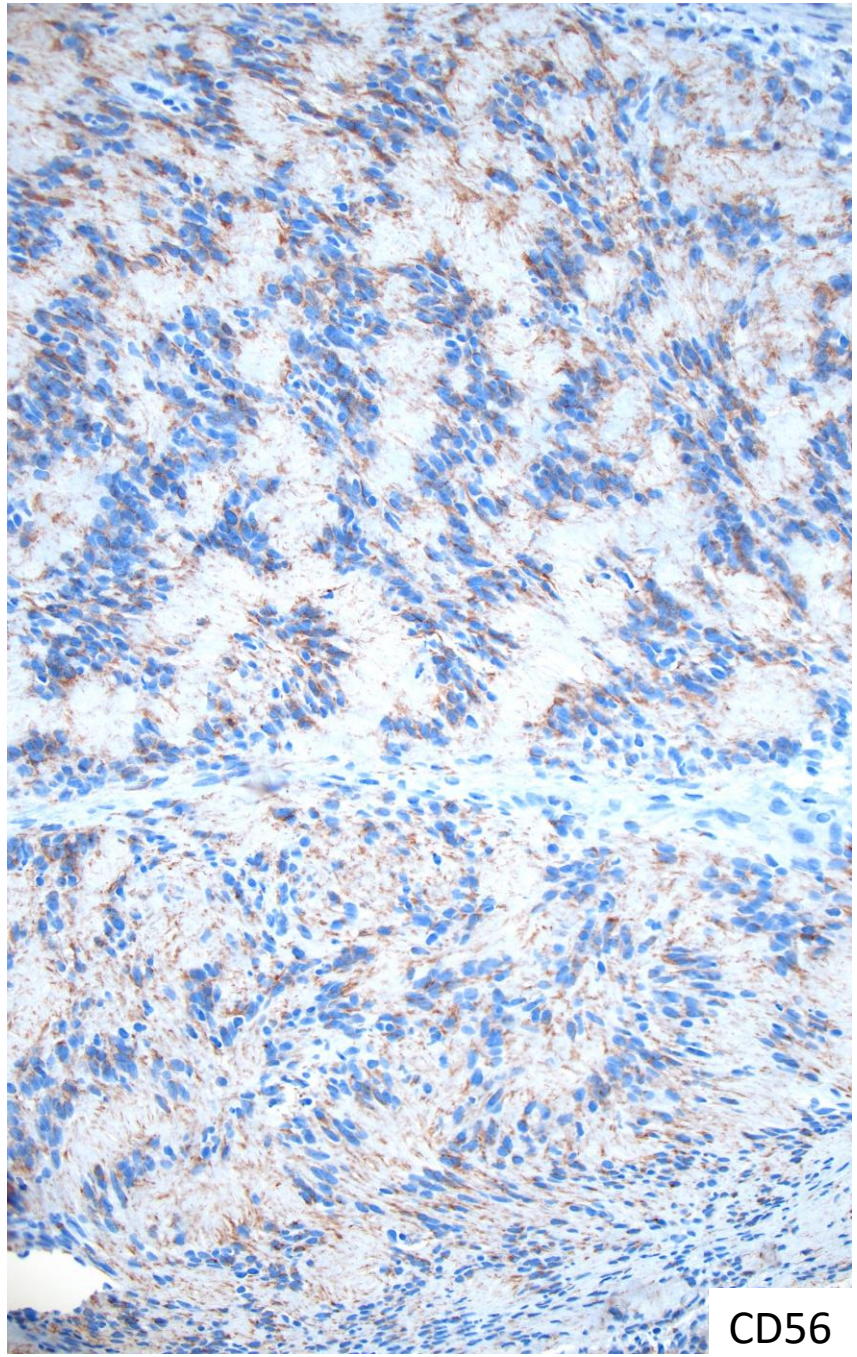
Theodor Schwann
1808-1882

http://t2.gstatic.com/images?q=tbn:ANd9GcSA0ing-IW4PkHSmhuh4QMtDfRWuLPX8gjXJu-tyklbhXVsaZzu-3iOUlwmxMJd

Schwannoma



SOX10



CD56

El neuroblastoma, conceptos actuales*

Asesor: Dr. Joaquín Carrillo Farga**
Miguel R. Reyes Mújica*
Eliezer Masliah Meyohas*
León Rosen Besthoff*

Los blastomas son neoplasias que tienen la apariencia del tejido embrionario del cual se originan. En muchos aspectos tienen más características de malformaciones pobremente organizadas que de neoplasias, sin embargo, el patrón de su comportamiento es maligno en la mayoría de los casos. Una característica de los blastomas es su capacidad para diferenciarse o madurar de manera similar a como un tejido embrionario se transforma en adulto. Esta capacidad permanece latente, pero puede manifestarse espontáneamente o bien ser inducida por el tratamiento.[1]

El neuroblastoma es una neoplasia maligna que puede originarse en cualquier parte del organismo en donde se encuentre tejido nervioso simpático.

Incidencia

Durante la primera mitad del presente siglo, las neoplasias malignas no se incluían dentro de las diez principales causas de muerte en los niños.[2] Estas en la actualidad ocupan el quinto lugar como causa de muerte en la niñez,[3] siendo las leucemias y linfomas los más frecuentes (50%), seguidos de los tumores de sistema nervioso (25%), y del nefroblastoma (20%); el 5% restante lo ocupan diversos tumores.[4]

Los tumores del sistema nervioso más frecuentes en los niños son: meduloblastomas, retinoblastomas y neuroblastomas.[4]

La incidencia del neuroblastoma se reporta con una tasa anual de 1 por 100 mil[5] en la población menor de 15 años. El 90 por ciento de estos tumores se presenta antes de los 10 años de edad.

Etiología

La causa que condiciona la aparición del neuroblastoma, lo mismo que en la mayoría de las neoplasias malignas, es desconocida. Algunos autores basándose en experimentos en el hamster postulan como agentes causales al citomegalovirus y al J C virus polioma.[6,7]

Es frecuente encontrar aberraciones cromosómicas en estos pacientes, lo que se correlaciona con la hipótesis de Knudson,[8,9] que propone como causas de una diferenciación celular errónea, diversas mutaciones genéticas, probablemente originadas por agentes físicos, químicos o biológicos (virus) con el consecuente desarrollo de un cáncer de células embrionarias (neuroblastoma). Entre las aberraciones más comúnmente encontradas en los cromosomas de estas células se menciona, de acuerdo a Brodeur,[10] la deleción 1p- (50% de los casos estudiados), y según Sandberg[11] la formación de los llamados cromosomas minutos esféricos dobles (40%).[12] Otras alteraciones menos frecuentes son: +6, +7, 9q+, 6q+, 10q+, 12q+, −13, 13p+, 16q+ y 22p+.[10]

Basándose en lo anterior, Prasad[13] propone que estas alteraciones cromosómicas afectan al gene que codifica la información para la síntesis de la fosfodiesterasa, provocando un aumento en la concentración de esta enzima y por lo consiguiente en la

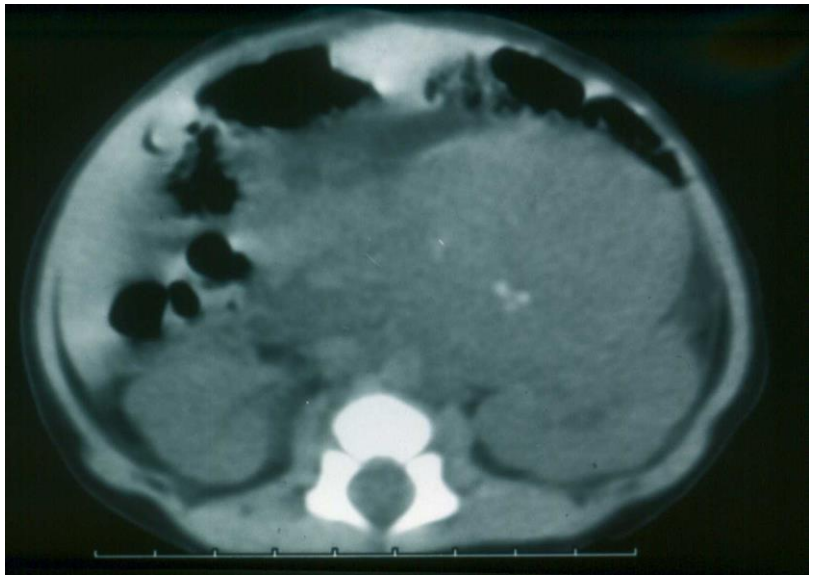
*VIII ciclo.
**Médico adscrito al Servicio de patología del Inst. Nac. de Pediatría D.I.F.
°Asignatura Neurología. Jurado calificador Dr. Manuel Irigoyen, Prof. titular de Neurología.

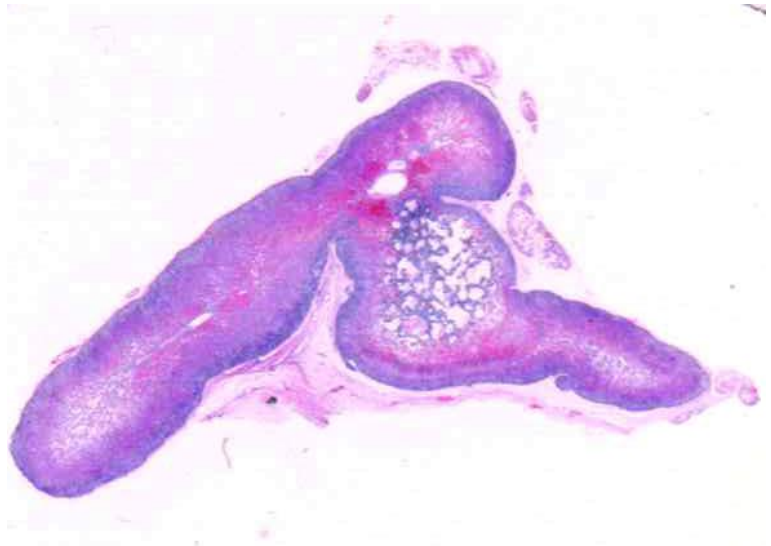
Neuroblastoma: current concepts (1981)

Reyes-Mújica M, Masliah ME, Rosen BL. El neuroblastoma, conceptos actuales. Rev Fac Med Mex XXIV(4):19-33,1981.

Neuroblastoma

Retroperitoneal

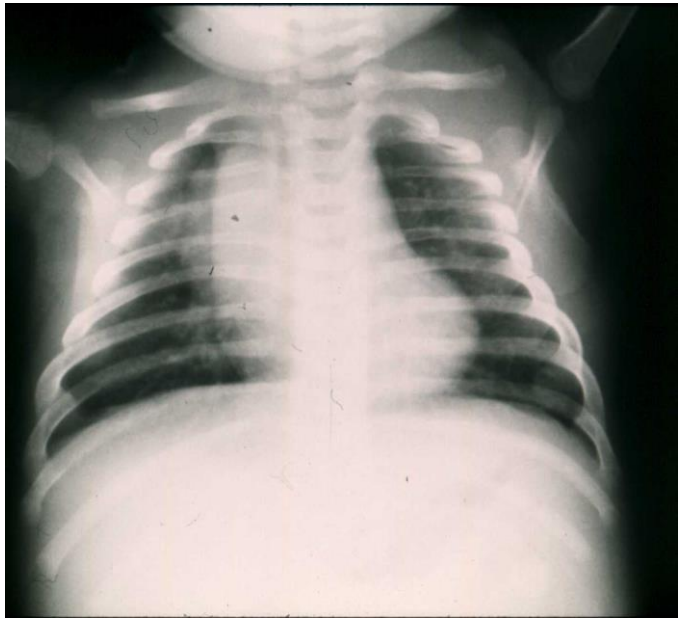


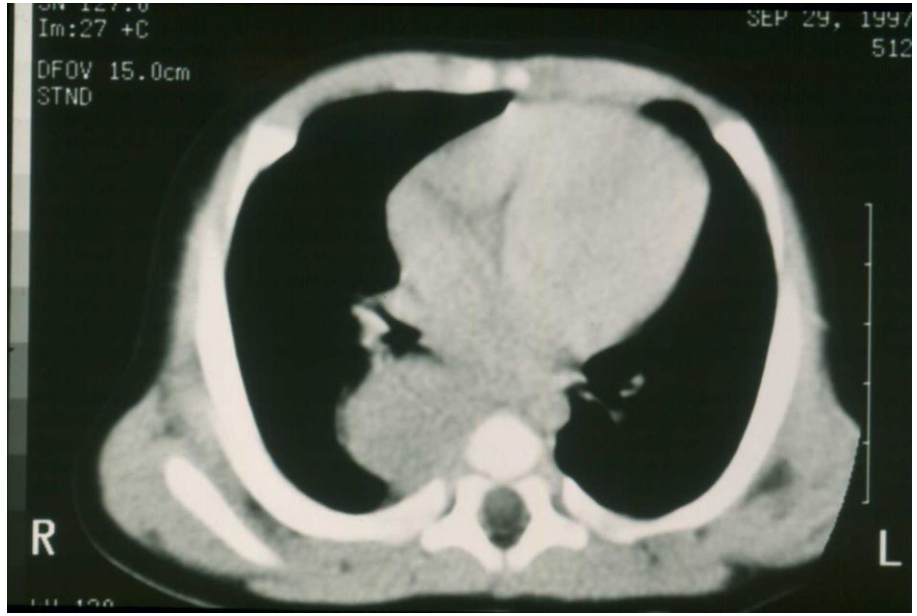


NBL *in situ:*
0.55%
in autopsies of
Patients below
3 months of age.

Beckwith JB, Perrin EV.
Am J Pathol 1963
PMID: 14099453

Mediastinal





A summary of the inaugural WHO Classification of Pediatric Tumors: Transitioning from the optical into the molecular era

Stefan M. Pfister[#,1,2,3], Miguel Reyes-Múgica[4], John K.C. Chan[5], Henrik Hasle[6], Alexander J. Lazar[7], Sabrina Rossi[8], Andrea Ferrari[9], Jason A. Jarzembowski[10], Kathy Pritchard-Jones[11], D. Ashley Hill[12], Thomas S. Jacques[13], Pieter Wesseling[14,15], Dolores López Terrada[16], Andreas von Deimling[17,18], Christian P. Kratz[19], Ian Cree[20] and Rita Alaggio[#,21]

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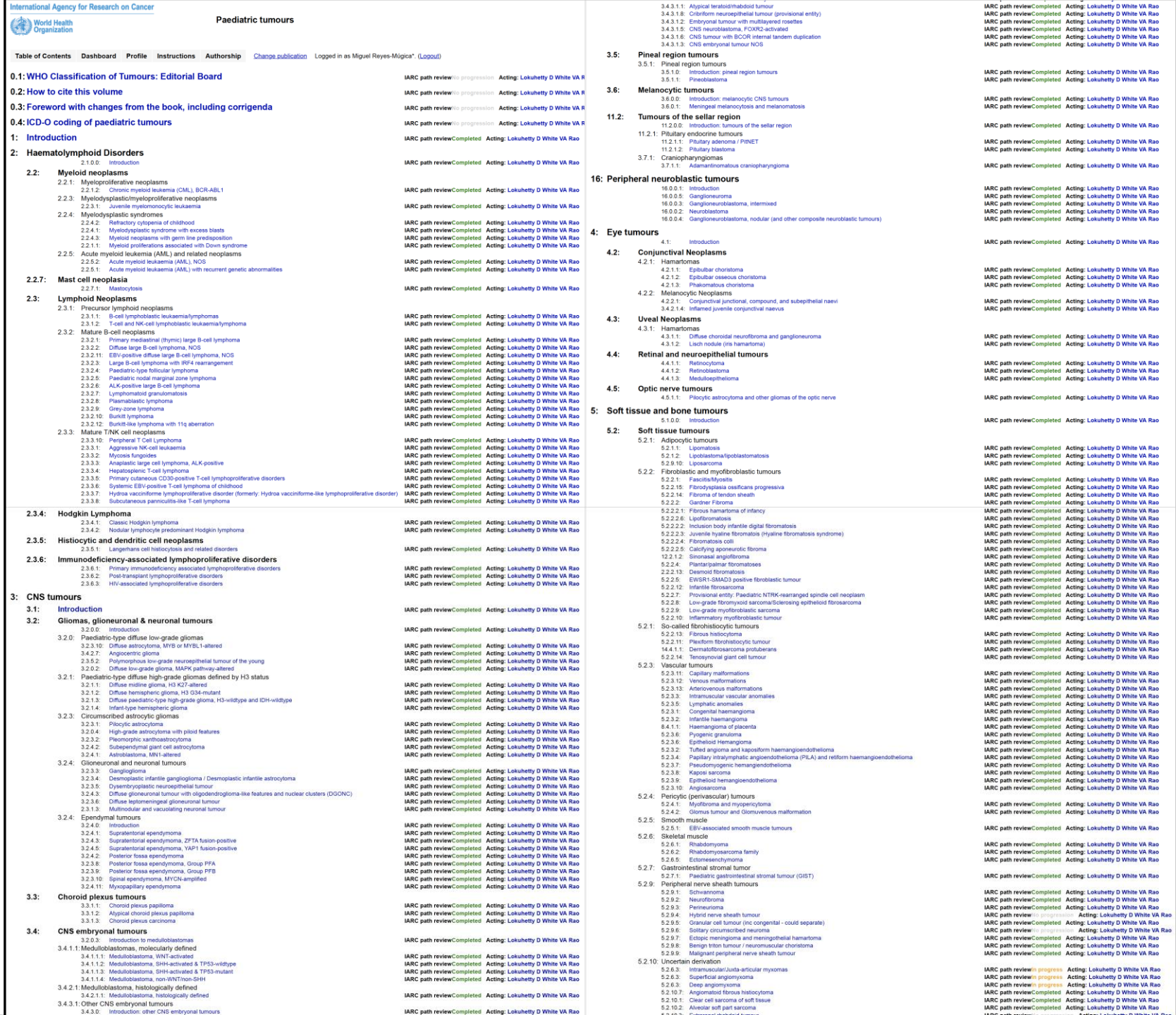

International Agency for Research on Cancer
World Health Organization

Paediatric tumours

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0.3: Foreword with changes from the book, including corrigenda — IARC path review no progression Acting: Lokuhetty D White VA R
0.4: ICD-O coding of paediatric tumours — IARC path review no progression Acting: Lokuhetty D White VA R
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2: Haematolymphoid Disorders
2.1.0.0: Introduction — IARC path review Completed Acting: Lokuhetty D White VA Rao
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2.2.1: Myeloproliferative neoplasms
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2.2.3.1: Juvenile myelomonocytic leukaemia — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.2.4: Myelodysplastic syndromes
2.2.4.2: Refractory cytopenia of childhood — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.2.4.1: Myelodysplastic syndrome with excess blasts — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.2.4.3: Myeloid neoplasms with germ line predisposition — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.2.1.1: Myeloid proliferations associated with Down syndrome — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.2.5: Acute myeloid leukemia (AML) and related neoplasms
2.2.5.2: Acute myeloid leukaemia (AML), NOS — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.2.5.1: Acute myeloid leukaemia (AML) with recurrent genetic abnormalities — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.2.7: Mast cell neoplasia
2.2.7.1: Mastocytosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3: Lymphoid Neoplasms
2.3.1: Precursor lymphoid neoplasms
2.3.1.1: B-cell lymphoblastic leukaemia/lymphomas — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.1.2: T-cell and NK-cell lymphoblastic leukaemia/lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2: Mature B-cell neoplasms
2.3.2.1: Primary mediastinal (thymic) large B-cell lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.2: Diffuse large B-cell lymphoma, NOS — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.11: EBV-positive diffuse large B-cell lymphoma, NOS — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.3: Large B-cell lymphoma with IRF4 rearrangement — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.4: Paediatric-type follicular lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.5: Paediatric nodal marginal zone lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.6: ALK-positive large B-cell lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.7: Lymphomatoid granulomatosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.8: Plasmablastic lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.9: Grey-zone lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.10: Burkitt lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.2.12: Burkitt-like lymphoma with 11q aberration — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3: Mature T/NK cell neoplasms
2.3.3.10: Peripheral T Cell Lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.1: Aggressive NK-cell leukaemia — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.2: Mycosis fungoides — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.3: Anaplastic large cell lymphoma, ALK-positive — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.4: Hepatosplenic T-cell lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.5: Primary cutaneous CD30-positive T-cell lymphoproliferative disorders — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.6: Systemic EBV-positive T-cell lymphoma of childhood — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.7: Hydroa vacciniforme lymphoproliferative disorder (formerly: Hydroa vacciniforme-like lymphoproliferative disorder) — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.3.8: Subcutaneous panniculitis-like T-cell lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.4: Hodgkin Lymphoma
2.3.4.1: Classic Hodgkin lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.4.2: Nodular lymphocyte predominant Hodgkin lymphoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.5: Histiocytic and dendritic cell neoplasms
2.3.5.1: Langerhans cell histiocytosis and related disorders — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.6: Immunodeficiency-associated lymphoproliferative disorders
2.3.6.1: Primary immunodeficiency associated lymphoproliferative disorders — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.6.2: Post-transplant lymphoproliferative disorders — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.6.3: HIV-associated lymphoproliferative disorders — IARC path review Completed Acting: Lokuhetty D White VA Rao
3: CNS tumours
3.1: Introduction — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2: Gliomas, glioneuronal & neuronal tumours
3.2.0.0: Introduction — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.0: Paediatric-type diffuse low-grade gliomas
3.2.3.10: Diffuse astrocytoma, MYB or MYBL1-altered — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.2.7: Angiocentric glioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.5.2: Polymorphous low-grade neuroepithelial tumour of the young — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.0.2: Diffuse low-grade glioma, MAPK pathway-altered — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.1: Paediatric-type diffuse high-grade gliomas defined by H3 status
3.2.1.1: Diffuse midline glioma, H3 K27-altered — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.1.2: Diffuse hemispheric glioma, H3 G34-mutant — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.1.3: Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.1.4: Infant-type hemispheric glioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3: Circumscribed astrocytic gliomas
3.2.3.1: Pilocytic astrocytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.0.4: High-grade astrocytoma with piloid features — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3.2: Pleomorphic xanthoastrocytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.2: Subependymal giant cell astrocytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.1: Astroblastoma, MN1-altered — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4: Glioneuronal and neuronal tumours
3.2.3.3: Ganglioglioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3.4: Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3.5: Dysembryoplastic neuroepithelial tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.3: Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (DGONC) — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3.6: Diffuse leptomeningeal glioneuronal tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
2.3.1.3: Multinodular and vacuolating neuronal tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4: Ependymal tumours
3.2.4.0: Introduction — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.1: Supratentorial ependymoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.3: Supratentorial ependymoma, ZFTA fusion-positive — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.5: Supratentorial ependymoma, YAP1 fusion-positive — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.2: Posterior fossa ependymoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3.8: Posterior fossa ependymoma, Group PFA — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3.9: Posterior fossa ependymoma, Group PFB — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.3.10: Spinal ependymoma, MYCN-amplified — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.2.4.11: Myxopapillary ependymoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.3: Choroid plexus tumours
3.3.1.1: Choroid plexus papilloma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.3.1.2: Atypical choroid plexus papilloma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.3.1.3: Choroid plexus carcinoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4: CNS embryonal tumours
3.2.0.3: Introduction to medulloblastomas — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.1.1: Medulloblastomas, molecularly defined
3.4.1.1.1: Medulloblastoma, WNT-activated — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.1.1.2: Medulloblastoma, SHH-activated & TP53-wildtype — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.1.1.3: Medulloblastoma, SHH-activated & TP53-mutant — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.1.1.4: Medulloblastoma, non-WNT/non-SHH — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.2.1: Medulloblastoma, histologically defined
3.4.2.1.1: Medulloblastoma, histologically defined — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.3.1: Other CNS embryonal tumours
3.4.3.0: Introduction: other CNS embryonal tumours — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.3.1.1: Atypical teratoid/rhabdoid tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.3.1.8: Cribriform neuroepithelial tumour (provisional entity) — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.3.1.2: Embryonal tumour with multilayered rosettes — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.3.1.5: CNS neuroblastoma, FOXR2-activated — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.3.1.6: CNS tumour with BCOR internal tandem duplication — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.3.1.3: CNS embryonal tumour NOS — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.5: Pineal region tumours
3.5.1: Pineal region tumours
3.5.1.0: Introduction: pineal region tumours — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.5.1.1: Pineoblastoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.6: Melanocytic tumours
3.6.0.0: Introduction: melanocytic CNS tumours — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.6.0.1: Meningeal melanocytosis and melanomatosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
11.2: Tumours of the sellar region
11.2.0.0: Introduction: tumours of the sellar region — IARC path review Completed Acting: Lokuhetty D White VA Rao
11.2.1: Pituitary endocrine tumours
11.2.1.1: Pituitary adenoma / PitNET — IARC path review Completed Acting: Lokuhetty D White VA Rao
11.2.1.2: Pituitary blastoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.7.1: Craniopharyngiomas
3.7.1.1: Adamantinomatous craniopharyngioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
16: Peripheral neuroblastic tumours
16.0.0.1: Introduction — IARC path review Completed Acting: Lokuhetty D White VA Rao
16.0.0.5: Ganglioneuroma — IARC path review Completed Acting: Lokuhetty D White VA Rao
16.0.0.3: Ganglioneuroblastoma, intermixed — IARC path review Completed Acting: Lokuhetty D White VA Rao
16.0.0.2: Neuroblastoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
16.0.0.4: Ganglioneuroblastoma, nodular (and other composite neuroblastic tumours) — IARC path review Completed Acting: Lokuhetty D White VA Rao
4: Eye tumours
4.1: Introduction — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.2: Conjunctival Neoplasms
4.2.1: Hamartomas
4.2.1.1: Epibulbar choristoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.2.1.2: Epibulbar osseous choristoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.2.1.3: Phakomatous choristoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.2.2: Melanocytic Neoplasms
4.2.2.1: Conjunctival junctional, compound, and subepithelial naevi — IARC path review Completed Acting: Lokuhetty D White VA Rao
3.4.2.1.4: Inflamed juvenile conjunctival naevus — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.3: Uveal Neoplasms
4.3.1: Hamartomas
4.3.1.1: Diffuse choroidal neurofibroma and ganglioneuroma — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.3.1.2: Lisch nodule (iris hamartoma) — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.4: Retinal and neuroepithelial tumours
4.4.1.1: Retinocytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.4.1.2: Retinoblastoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.4.1.3: Medulloepithelioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
4.5: Optic nerve tumours
4.5.1.1: Pilocytic astrocytoma and other gliomas of the optic nerve — IARC path review Completed Acting: Lokuhetty D White VA Rao
5: Soft tissue and bone tumours
5.1.0.0: Introduction — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2: Soft tissue tumours
5.2.1: Adipocytic tumours
5.2.1.1: Lipomatosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.1.2: Lipoblastoma/lipoblastomatosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9.10: Liposarcoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2: Fibroblastic and myofibroblastic tumours
5.2.2.1: Fasciitis/Myositis — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.15: Fibrodysplasia ossificans progressiva — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.14: Fibroma of tendon sheath — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.2: Gardner Fibroma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.2.1: Fibrous hamartoma of infancy — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.2.6: Lipofibromatosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.2.2: Inclusion body infantile digital fibromatosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.2.3: Juvenile hyaline fibromatosis (Hyaline fibromatosis syndrome) — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.2.4: Fibromatosis colli — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.2.5: Calcifying aponeurotic fibroma — IARC path review Completed Acting: Lokuhetty D White VA Rao
12.2.1.2: Sinonasal angiofibroma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.4: Plantar/palmar fibromatoses — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.13: Desmoid fibromatosis — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.5: EWSR1-SMAD3 positive fibroblastic tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.12: Infantile fibrosarcoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.7: Provisional entity: Paediatric NTRK-rearranged spindle cell neoplasm — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.8: Low-grade fibromyxoid sarcoma/Sclerosing epithelioid fibrosarcoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.9: Low-grade myofibroblastic sarcoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.10: Inflammatory myofibroblastic tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.1: So-called fibrohistiocytic tumours
5.2.2.13: Fibrous histiocytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.11: Plexiform fibrohistiocytic tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
14.4.1.1: Dermatofibrosarcoma protuberans — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.2.14: Tenosynovial giant cell tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3: Vascular tumours
5.2.3.11: Capillary malformations — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.12: Venous malformations — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.13: Arteriovenous malformations — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.3: Intramuscular vascular anomalies — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.5: Lymphatic anomalies — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.1: Congenital haemangioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.2: Infantile haemangioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
8.4.1.1: Haemangioma of placenta — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.6: Pyogenic granuloma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.6: Epithelioid Hemangioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.2: Tufted angioma and kaposiform haemangioendothelioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.4: Papillary intralymphatic angioendothelioma (PILA) and retiform haemangioendothelioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.7: Pseudomyogenic hemangioendothelioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.8: Kaposi sarcoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.9: Epithelioid hemangioendothelioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.3.10: Angiosarcoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.4: Pericytic (perivascular) tumours
5.2.4.1: Myofibroma and myopericytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.4.2: Glomus tumour and Glomuvenous malformation — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.5: Smooth muscle
5.2.5.1: EBV-associated smooth muscle tumours — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.6: Skeletal muscle
5.2.6.1: Rhabdomyoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.6.2: Rhabdomyosarcoma family — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.6.5: Ectomesenchymoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.7: Gastrointestinal stromal tumor
5.2.7.1: Paediatric gastrointestinal stromal tumour (GIST) — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9: Peripheral nerve sheath tumours
5.2.9.1: Schwannoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9.2: Neurofibroma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9.3: Perineurioma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9.4: Hybrid nerve sheath tumour — IARC path review no progression Acting: Lokuhetty D White VA Rao
5.2.9.5: Granular cell tumour (inc congenital - could separate) — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9.6: Solitary circumscribed neuroma — IARC path review no progression Acting: Lokuhetty D White VA Rao
5.2.9.7: Ectopic meningioma and meningothelial hamartoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9.8: Benign triton tumour / neuromuscular choristoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.9.9: Malignant peripheral nerve sheath tumour — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.10: Uncertain derivation
5.2.6.3: Intramuscular/Juxta-articular myxomas — IARC path review in progress Acting: Lokuhetty D White VA Rao
5.2.6.3: Superficial angiomyxoma — IARC path review in progress Acting: Lokuhetty D White VA Rao
5.2.6.3: Deep angiomyxoma — IARC path review in progress Acting: Lokuhetty D White VA Rao
5.2.10.7: Angiomatoid fibrous histiocytoma — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.10.1: Clear cell sarcoma of soft tissue — IARC path review Completed Acting: Lokuhetty D White VA Rao
5.2.10.2: Alveolar soft part sarcoma — IARC path review Completed Acting: Lokuhetty D White VA Rao

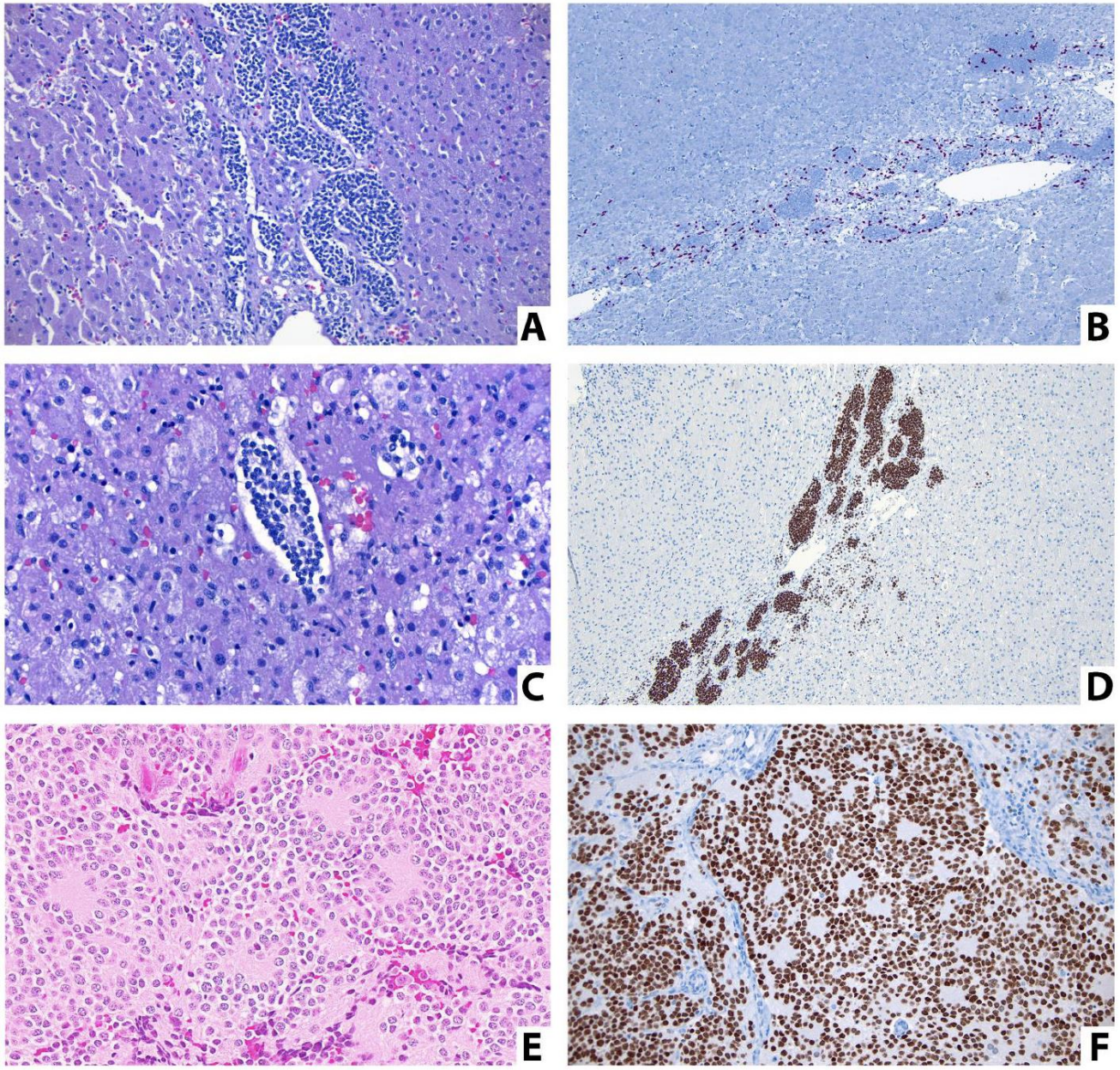
General aspects

- Peripheral Neuroblastic Tumours (PNTs) belong to the sympathoadrenal lineage of neural crest-derived tissues.
- “Neuroblastoma” is an all-encompassing term for pNTs.
- Four categories, according to the International Neuroblastoma Pathology Committee:
  - Ganglioneuroma (Schwannian stroma-dominant)
  - Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)
  - Ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-dominant and stroma-poor)
  - Neuroblastoma (Schwannian stroma-poor)

Classification of “Other” solid tumors

- We have taken the *developmental* approach as much as possible.
- Children are developing organisms, undergoing multiple and marked changes at a speed often inversely proportional to the age of the patient
- Congenital and neonatal tumors occur in immature tissues, where the histological similarities between fetal structures and their neoplastic counterparts may not be immediately obvious: the “Blastomas”:
  - Neuroblastoma, nephroblastoma, hepatoblastoma, pancreatoblastoma, gastroblastoma.

Figure 2: Developmental trajectories of pediatric solid tumors



A to D: Fetal adrenal gland at 21-22 weeks of gestation.

A) Migrating neural crest cells penetrate through the mesodermally-derived fetal adrenal cortex homing into the future adrenal medulla (H&E; original magnification 200X).

B) SOX10 immunohistochemical stain highlights the nuclei of migrating neural crest cells at the periphery of the migratory clusters, representing future Schwann cell precursors (SOX10 immunohistochemistry; original magnification 100X).

C) Migrating neural crest cells forming a Homer Wright rosette, indistinguishable from a similar structure in a poorly differentiated neuroblastoma (see E & F). Note the fine cytoplasmic prolongations of the future adrenal medullary cells in the centre of the rosette (H&E; original magnification 400X).

D) PHOX2B immunohistochemical stain showing strong nuclear reactivity in the migrating neural crest cells of the future foetal adrenal medulla (PHOX2B immunohistochemistry; original magnification 100X).

E and F: Poorly differentiated neuroblastoma from a 1-year-old patient.

E) Several Homer Wright rosettes are seen with their characteristic central area of neuropil (H&E; original magnification 400X). F) PHOX2B immuno-histochemical stain highlighting the nuclei of the neoplastic neural crest cells (neuroblasts) in multiple Homer Wright rosettes (PHOX2B immunohistochemistry; original magnification 200X)

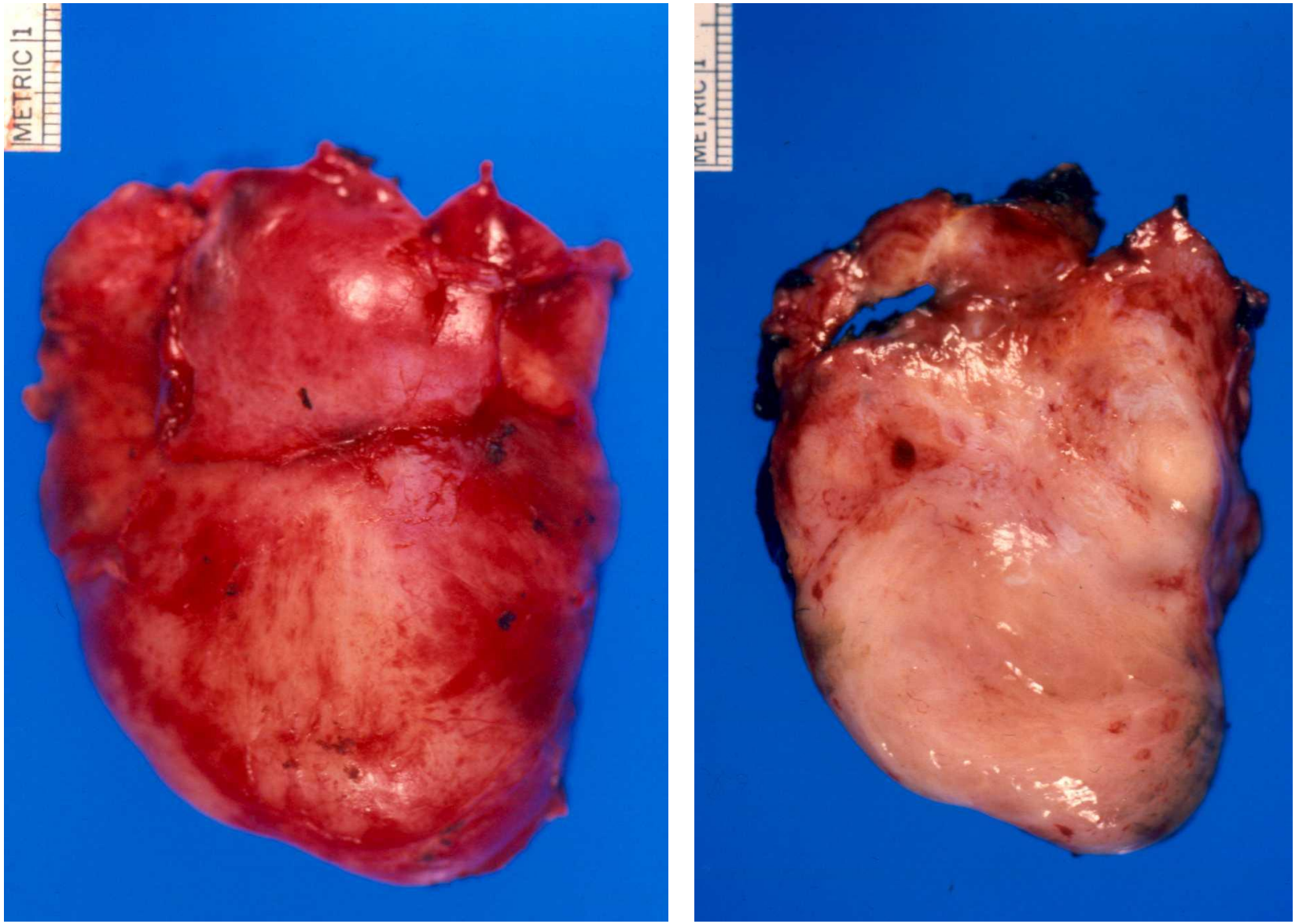
Pediatric Peripheral Neuroblastic Tumor Spectrum

Ganglioneuroma | Ganglioneuroblastoma intermixed | Ganglioneuroblastoma nodular | Neuroblastoma

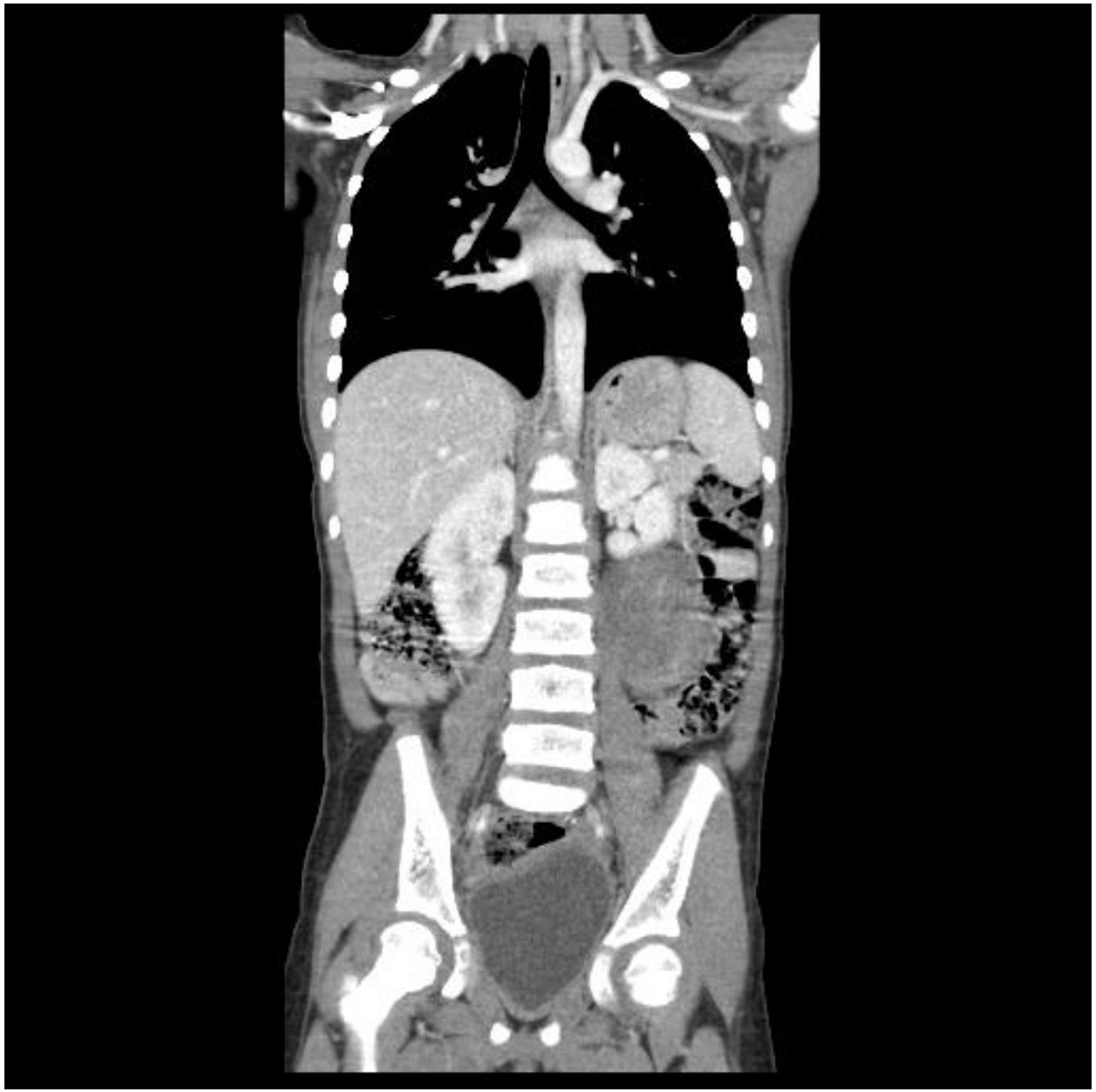
Ganglioneuroma

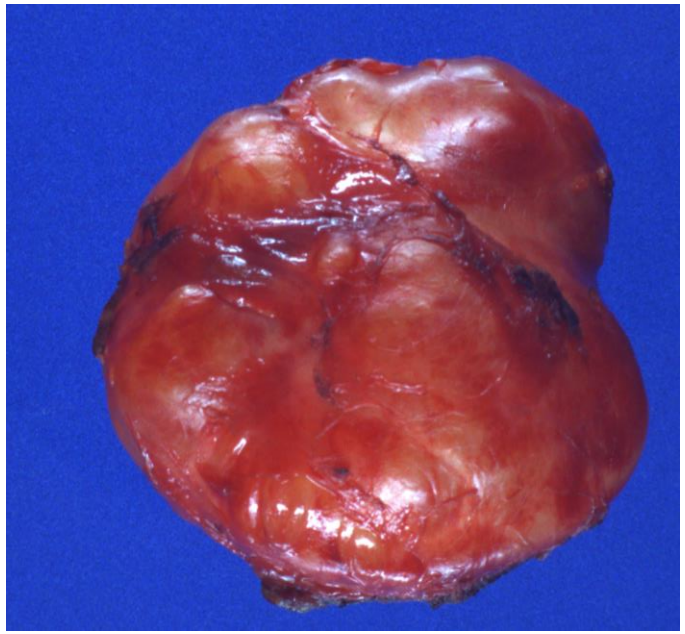
- Benign end of the spectrum.
- Composed of Schwann cells with scattered ganglion cells.
- Two variants:
  - Mature: all ganglion cells are fully mature.
  - Maturing: some ganglion cells show mild immaturity features.
- Most common in thorax. Metastasis of previous neuroblastoma with maturation may present is unusual sites.
- Most are incidental discoveries. Non-functional hormonally.
- More frequent in older children (median age of 6 years) and young adults.
- Interactions between ganglion cells and Schwann cells are thought to explain the mature appearance and benign behavior.
- Currently, all ganglioneuromas are thought to have been neuroblastomas which progressed toward maturation

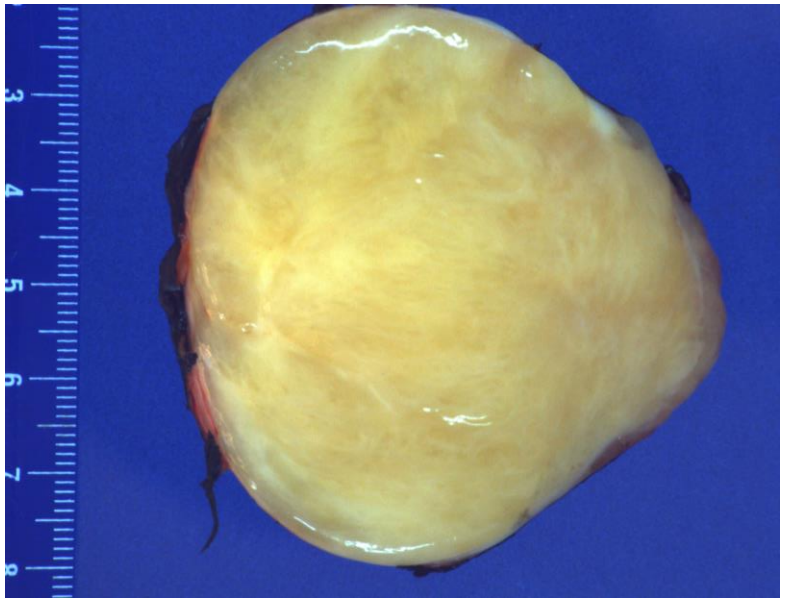
Ganglioneuroma



Ganglioneuroma

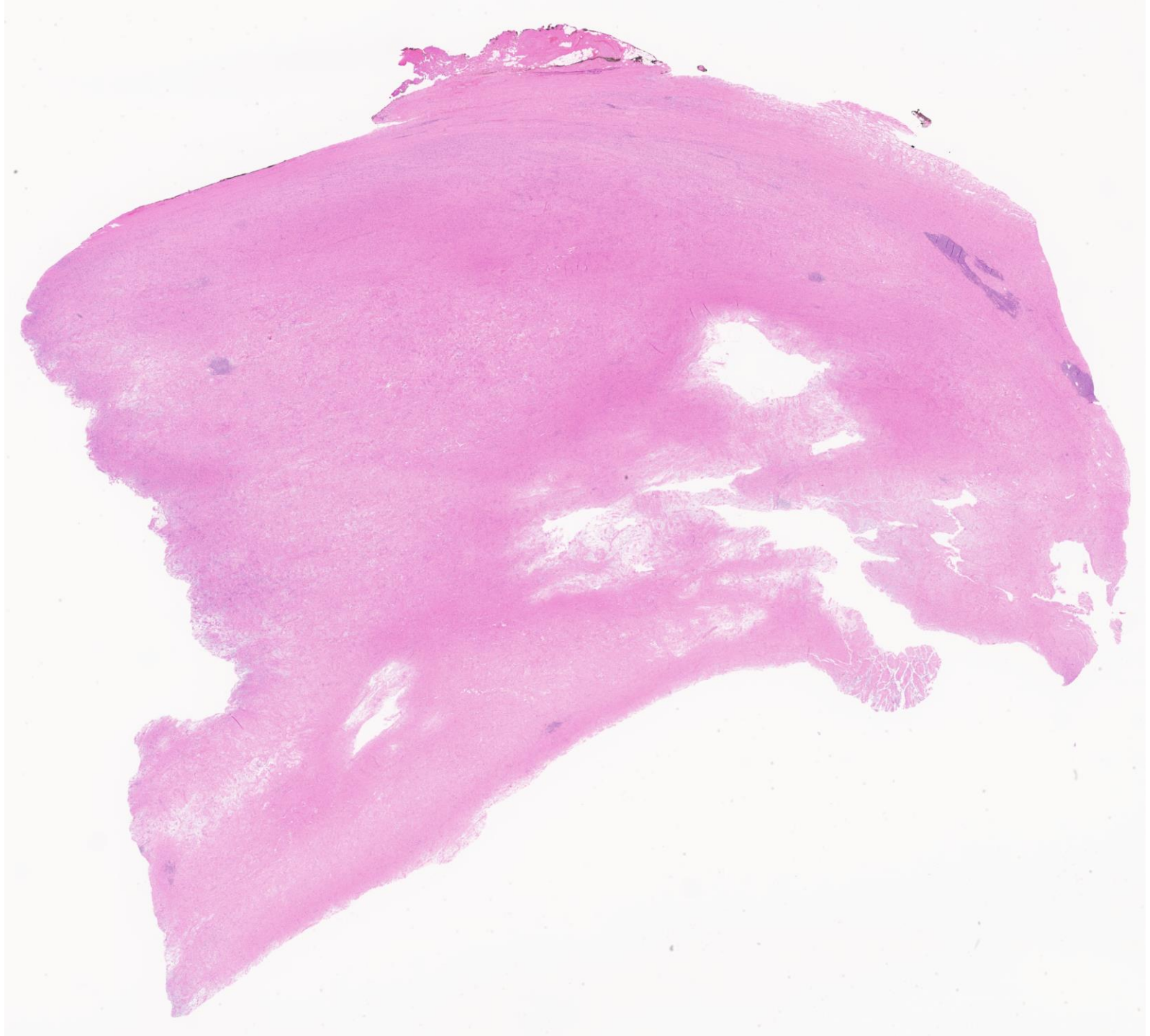


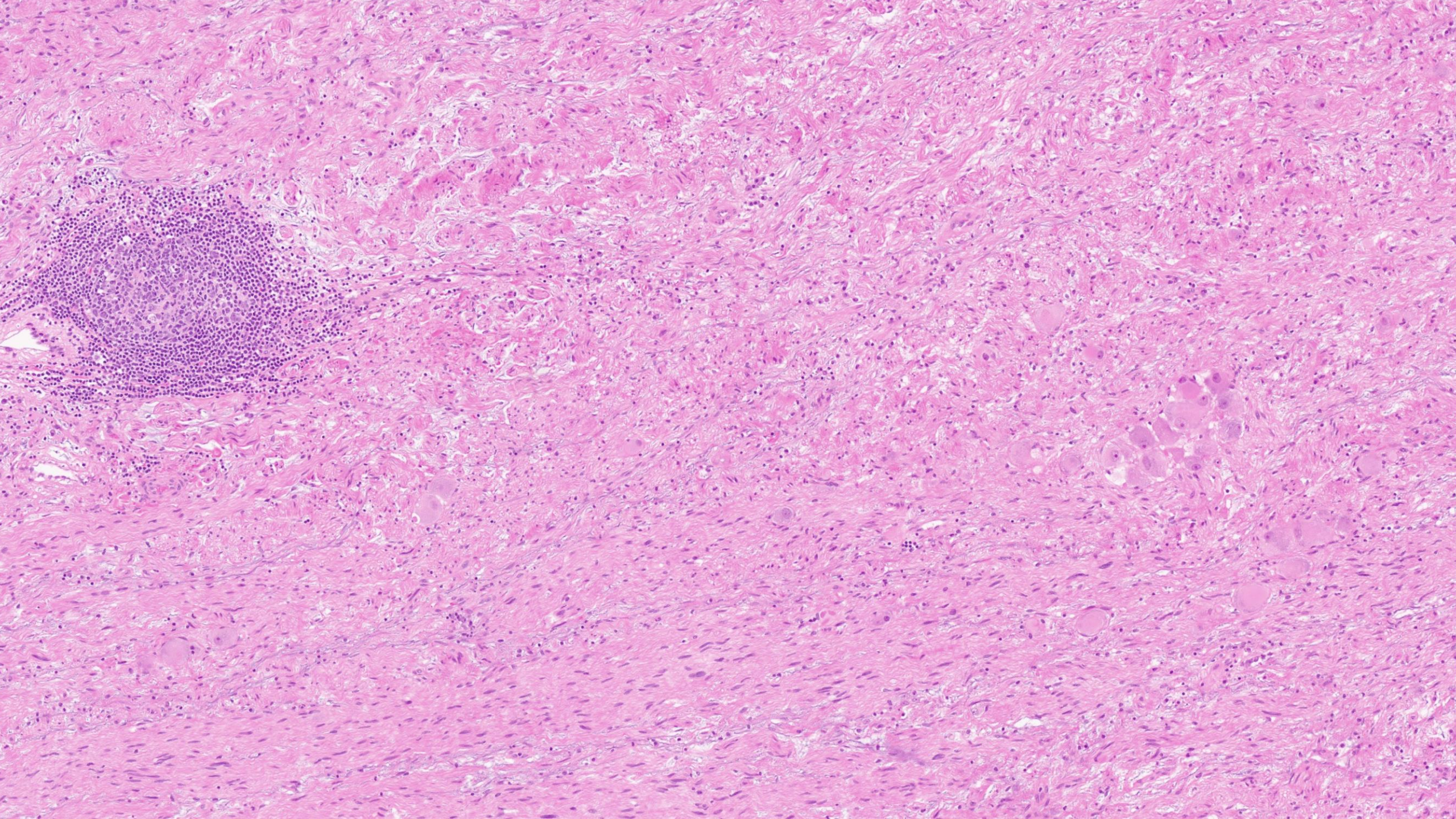


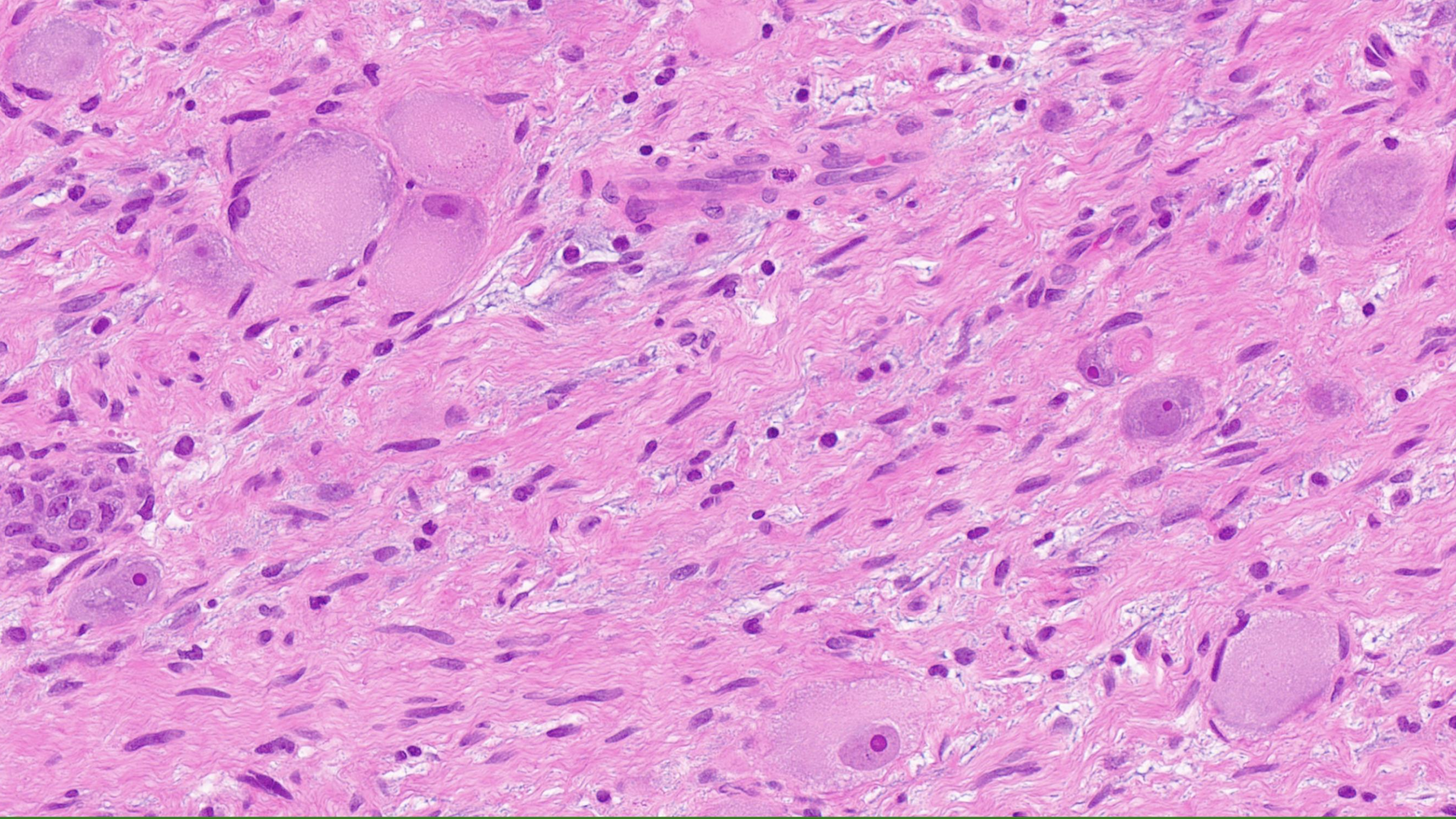


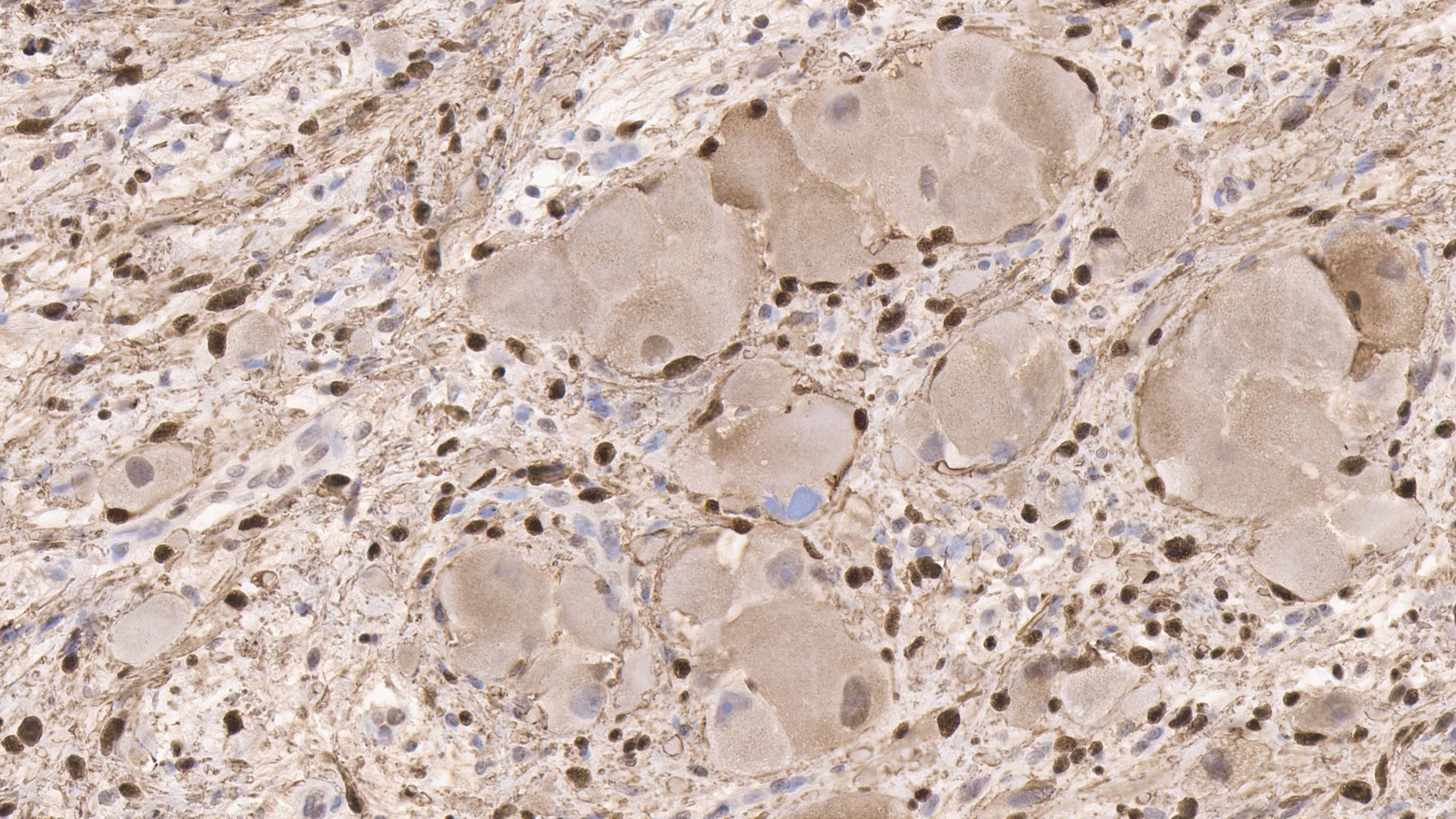
Ganglioneuroma Histology

- Different from GN in the soft tissue counterpart (moving target).
- >50% of tumor is composed of sheets or fascicles with well differentiated Schwann cells.
- Focal or small groups of mature/maturing ganglion cells.
  - Maturing ganglion cells: variable size; occasionally multinucleated.
  - Rare neuroblasts with signs of maturation without nesting.
  - No neuropil.
  - Mature ganglion cells surrounded by amphicytes (capsular or satellite cells).
  - Common foci of lymphocytes.
  - No mitotic activity.









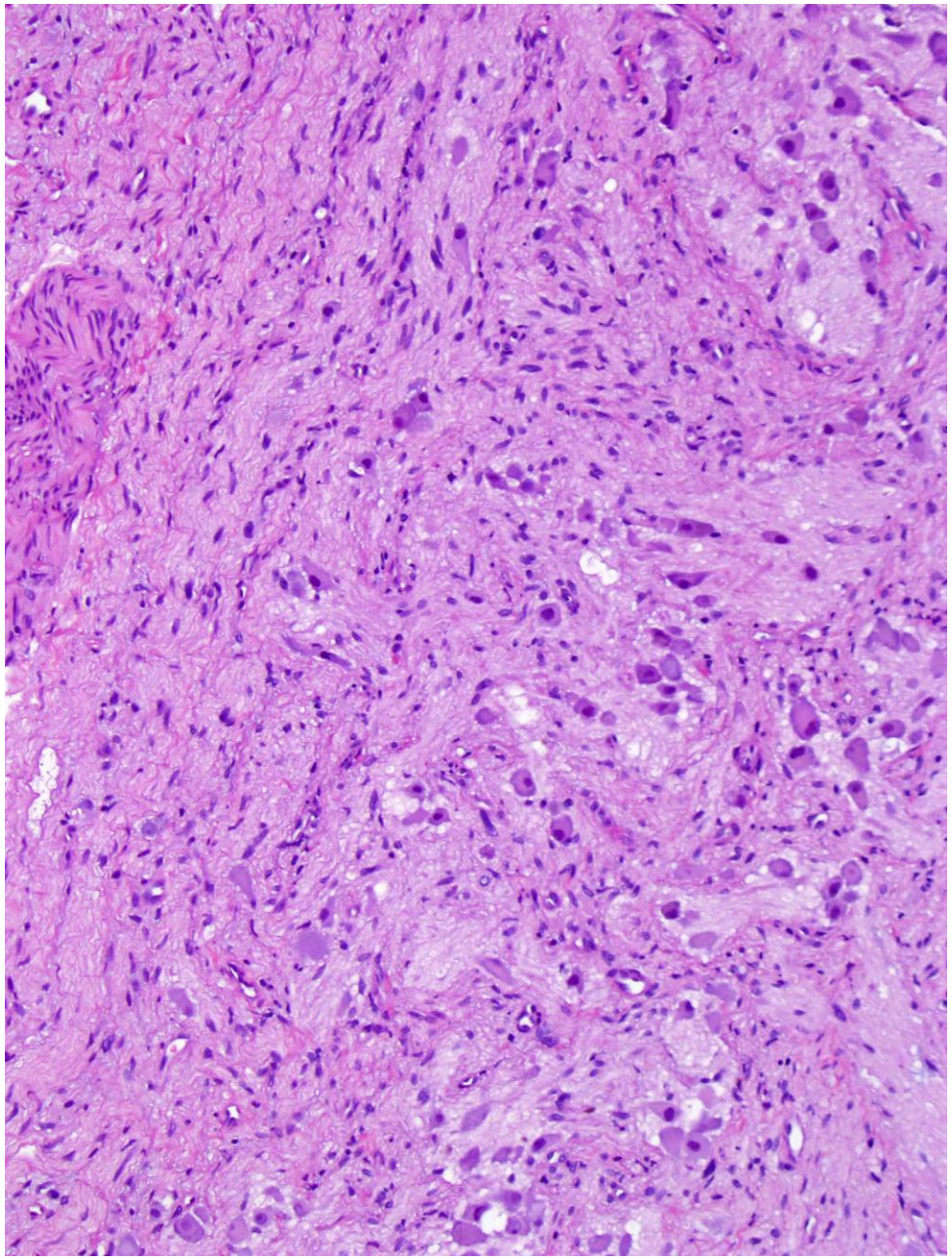
Ganglioneuroblastoma Intermixed

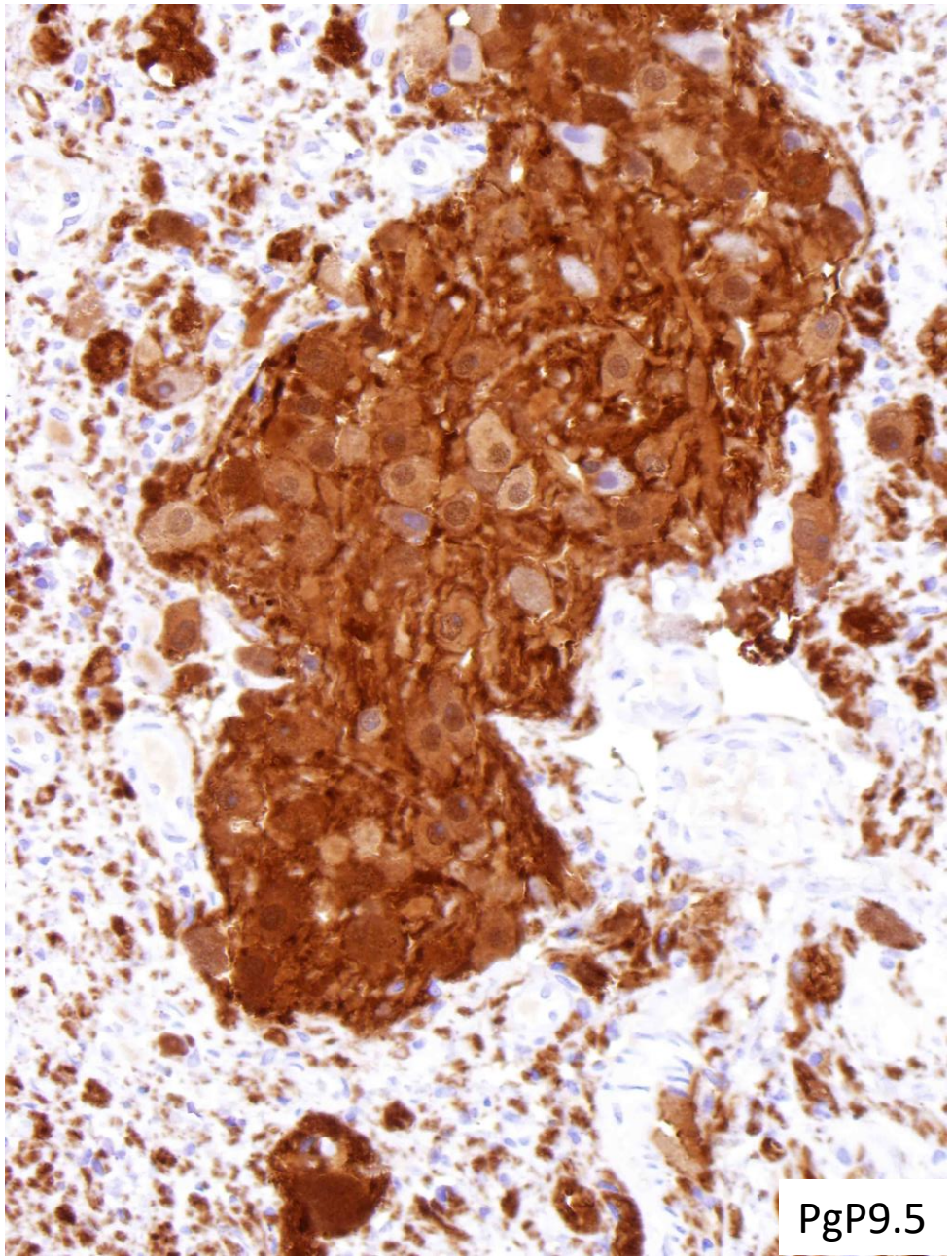
- Peripheral neuroblastic tumour at the middle point of the neuroblastic tumor spectrum.
- Also known as “Schwannian stroma-rich intermixed tumor”
- Predominantly in abdomen/retroperitoneum (adrenal). May occur in many other locations of sympathetic nature.
- Predominantly older children (median age is 6 YO).
- Most are not hormonally active
- Neuroblastomas may mature into GNB.
- GN and GNB represent 25% of peripheral neuroblastic tumors.
- Considered low-risk, with low metastasizing potential, but not sensitive to chemotherapy.

Ganglioneuroblastoma, intermixed Histology

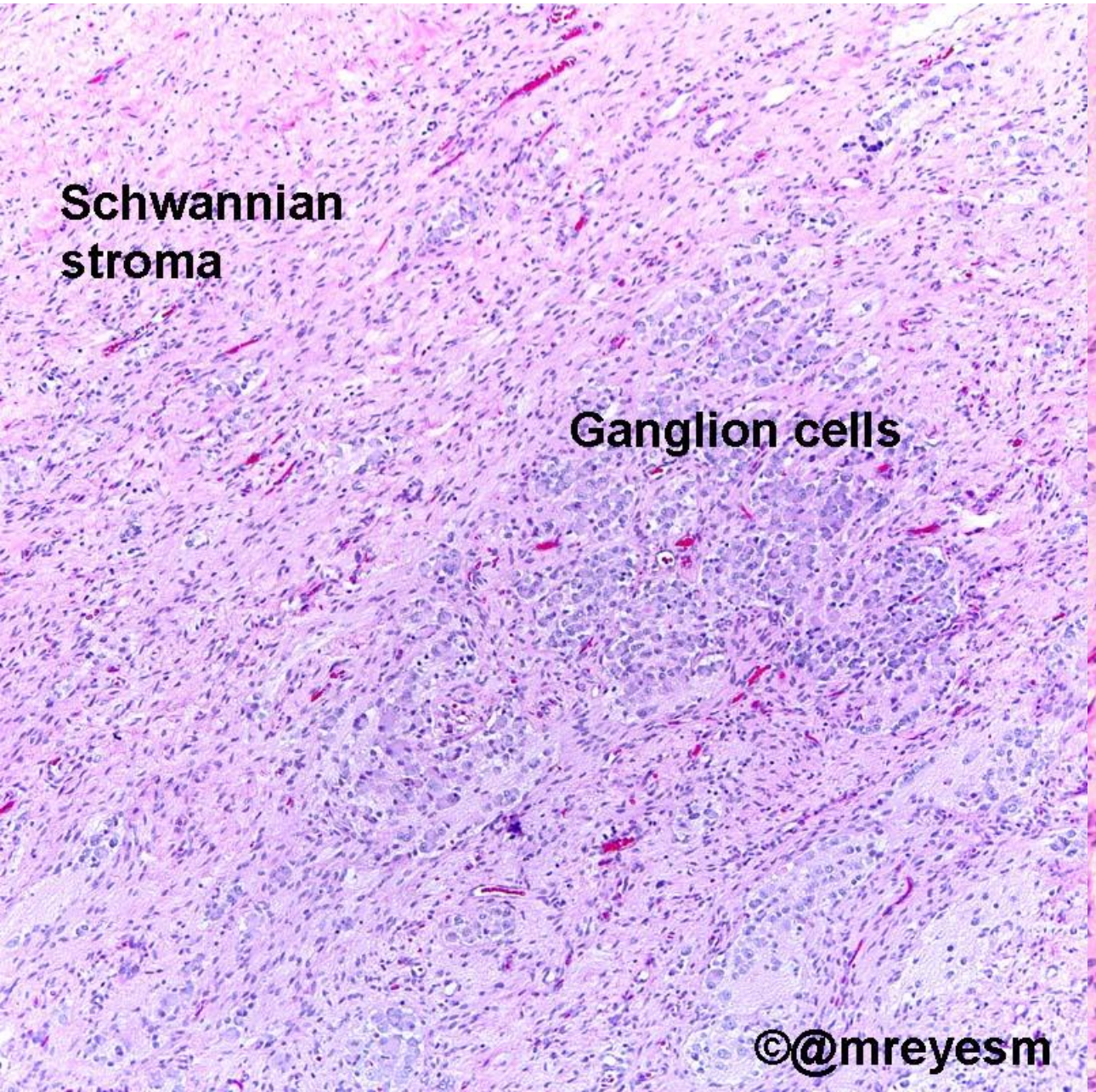
- Abundant (>50% of tumor) Schwannian stroma (ganglioneuromatous component)
- Scattered foci of neuroblasts with variable degrees of maturation.
- Well-defined clusters of neuroblasts set in neuropil surrounded by Schwannian stroma and variably maturing/mature ganglion cells.
- The different components are mixed without particular separation from one another (intermixed).
- Touch preps reveal ganglion cells, neurooblasts and Schwann cells.
- Rare *MYCN* amplification (<1%).
- Neuroblasts may show chromosomal aberrations
- Most are diploid due to abundant stroma.

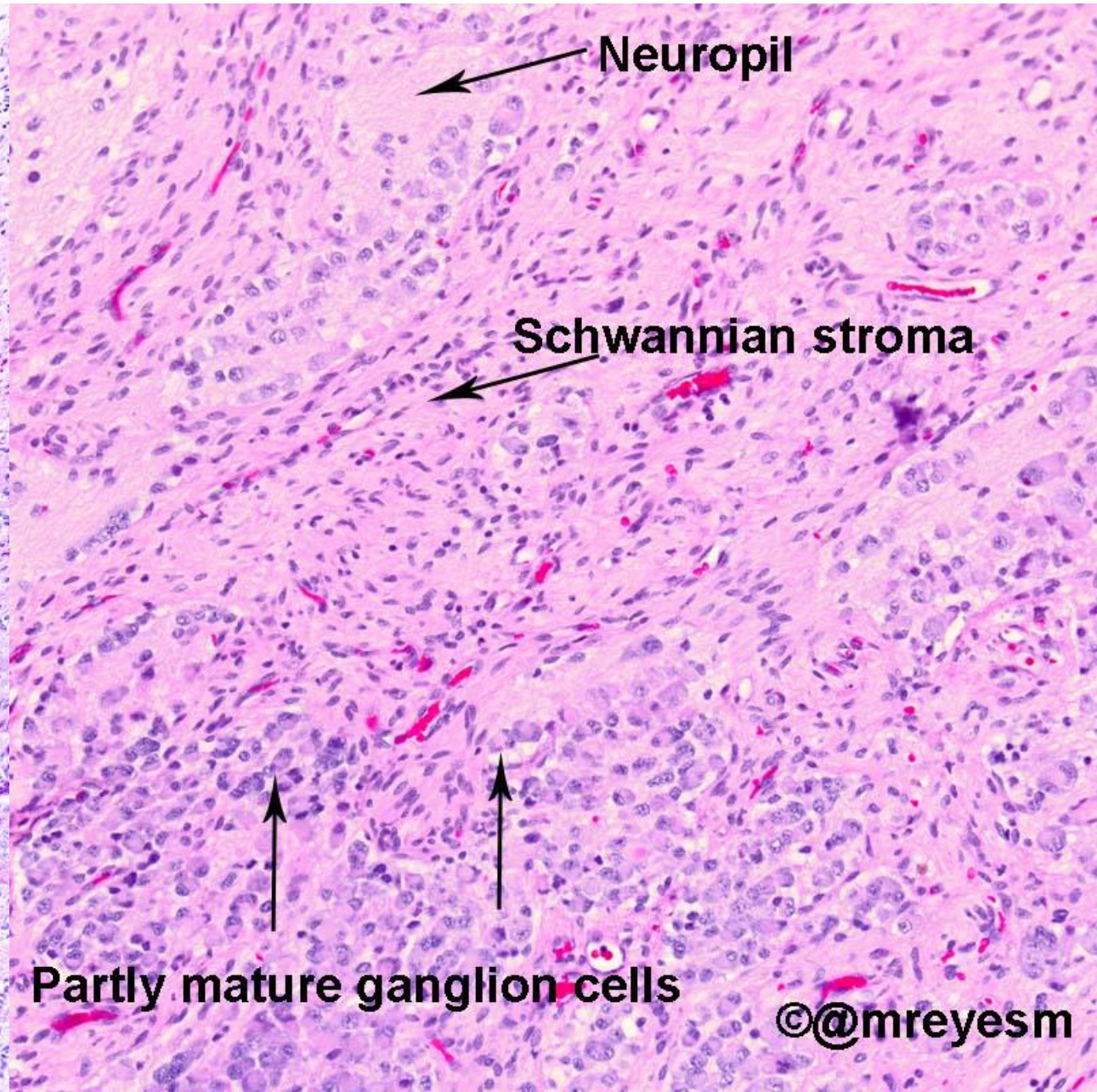
Ganglioneuroblastoma, intermixed





Ganglioneuroblastoma

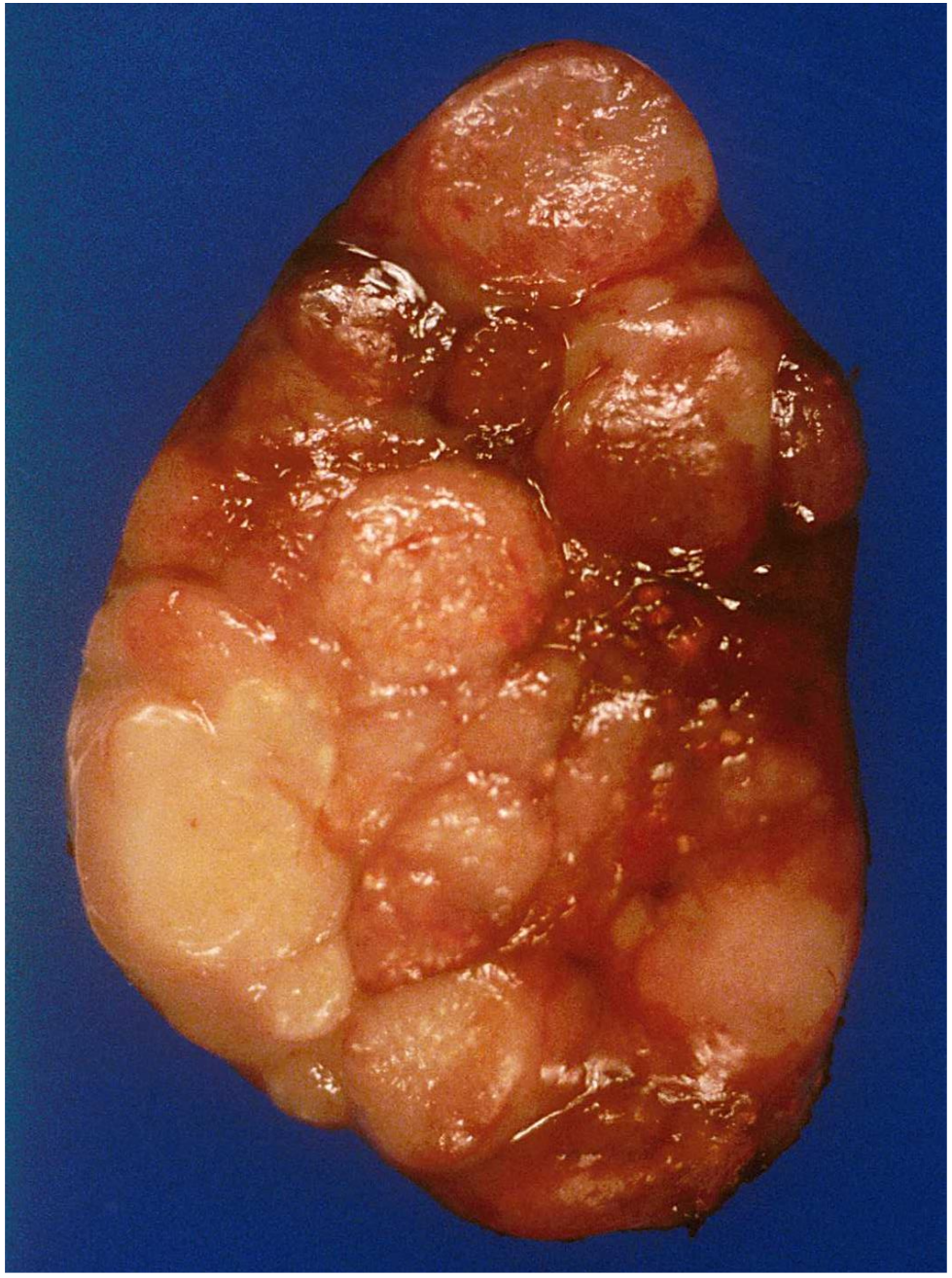


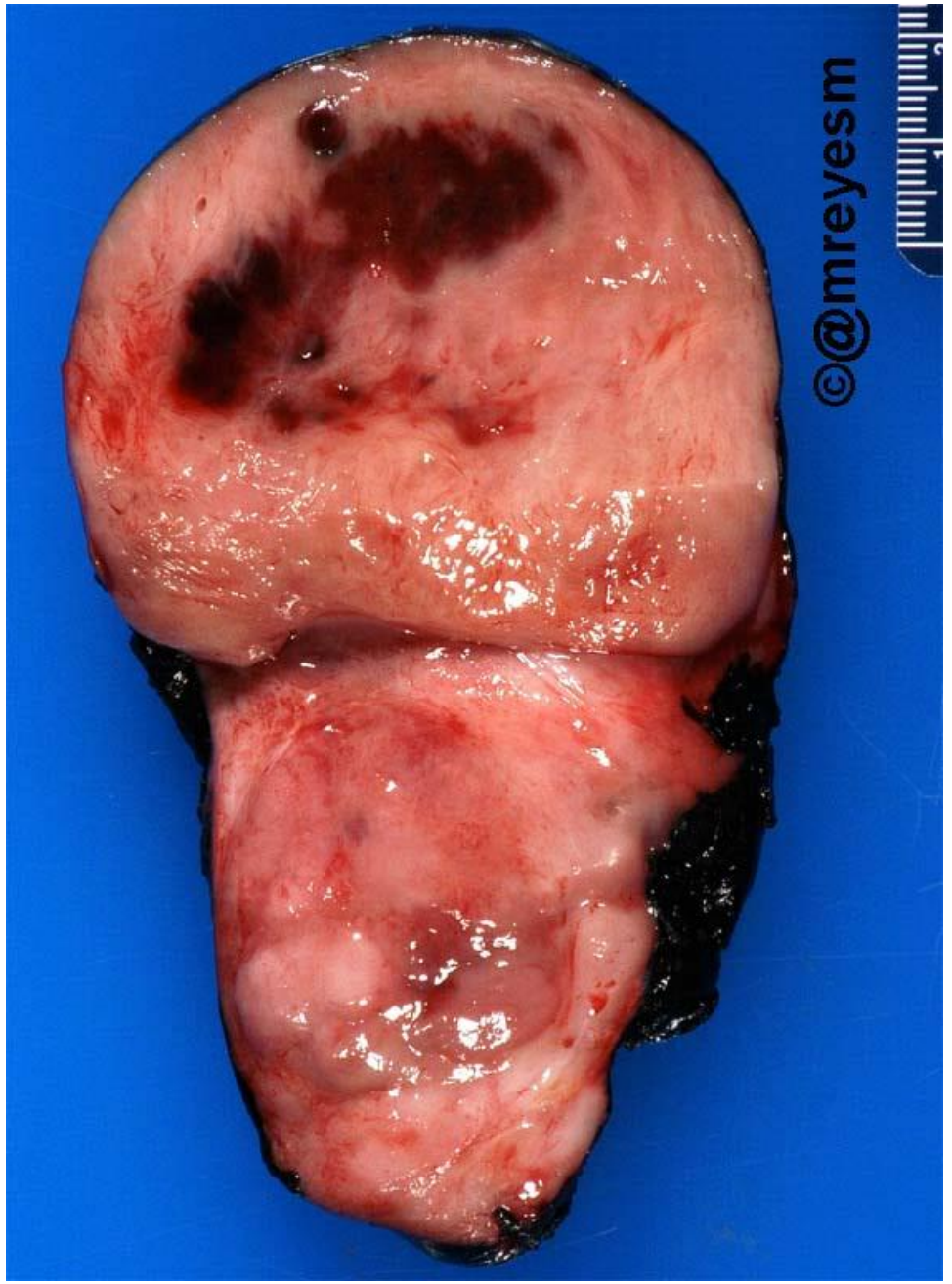


Ganglioneuroblastoma, nodular and other composite neuroblastic tumors.

- Not recommended: composite ganglioneuroblastoma.
- Location is similar to other PNTs.
- Frequently presents in the abdomen. May have extensive metastases.
- GNBn represents 5-10% of PNTs.
- Most patients are above 18 months of age. May occur in adults.
- Some authors believe that the nodule(s) represent clones with additional genetic abnormalities, but this is still not confirmed.

Ganglioneuroblastoma, nodular

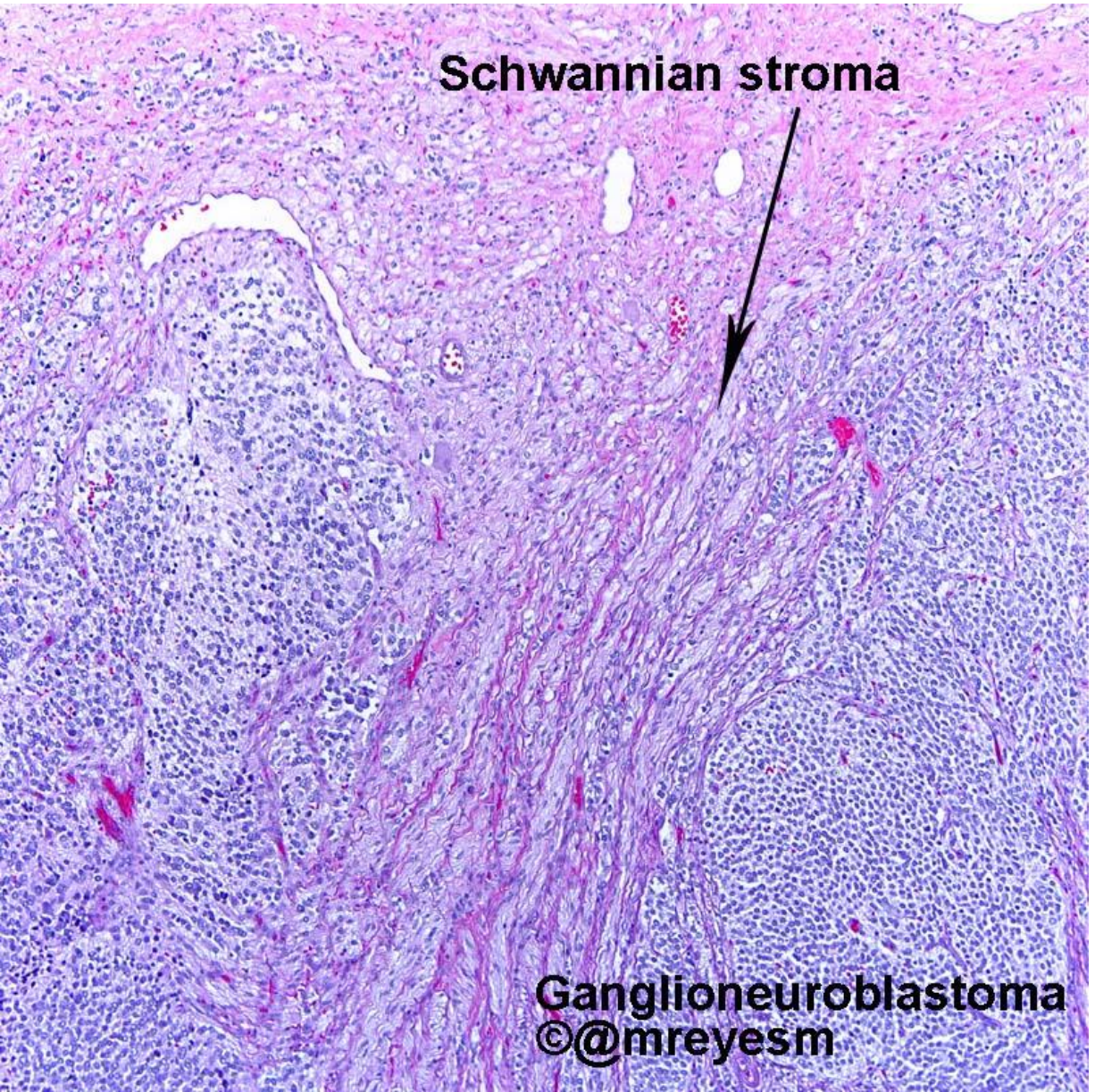


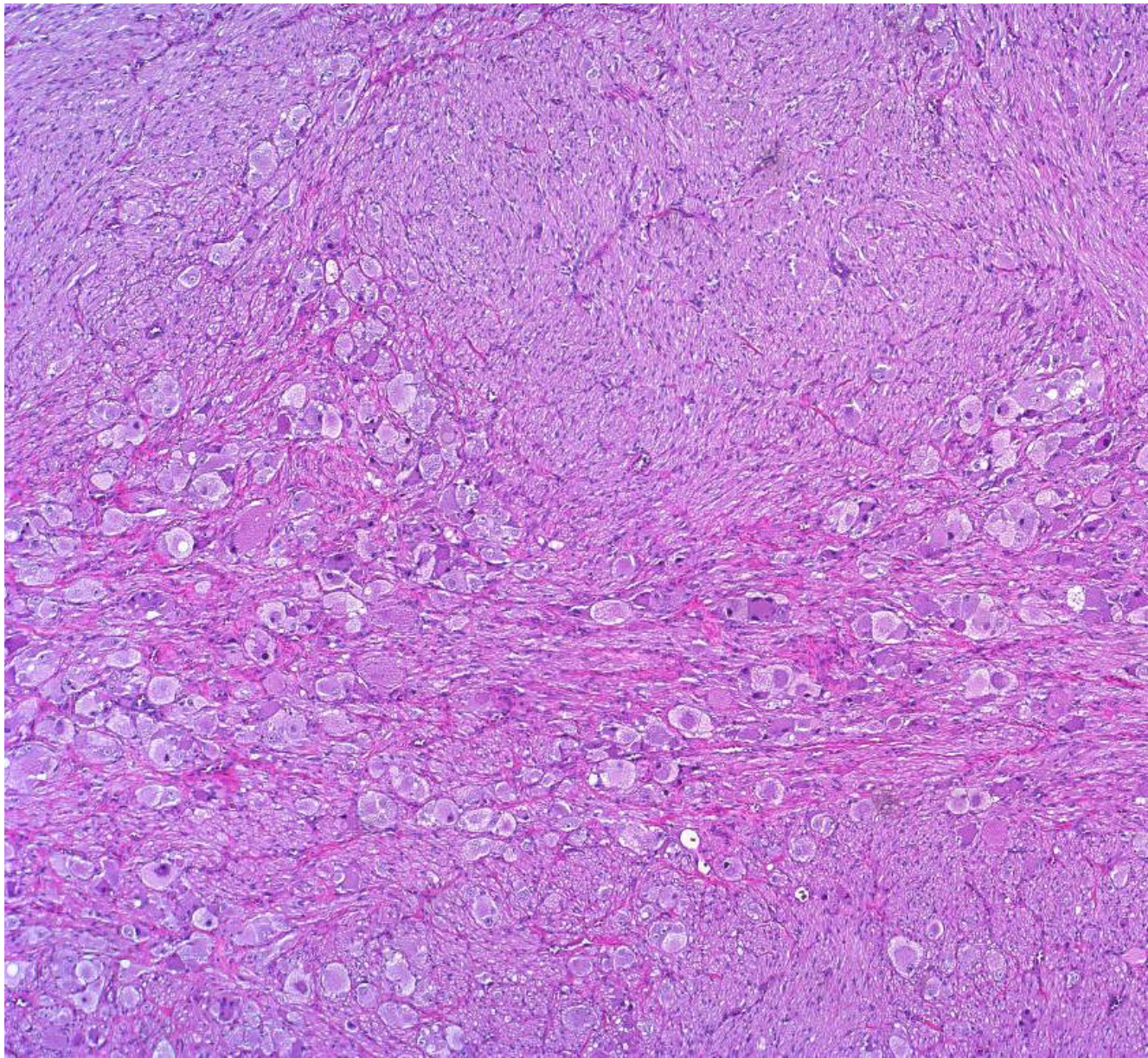


Ganglioneuroblastoma, nodular Histology

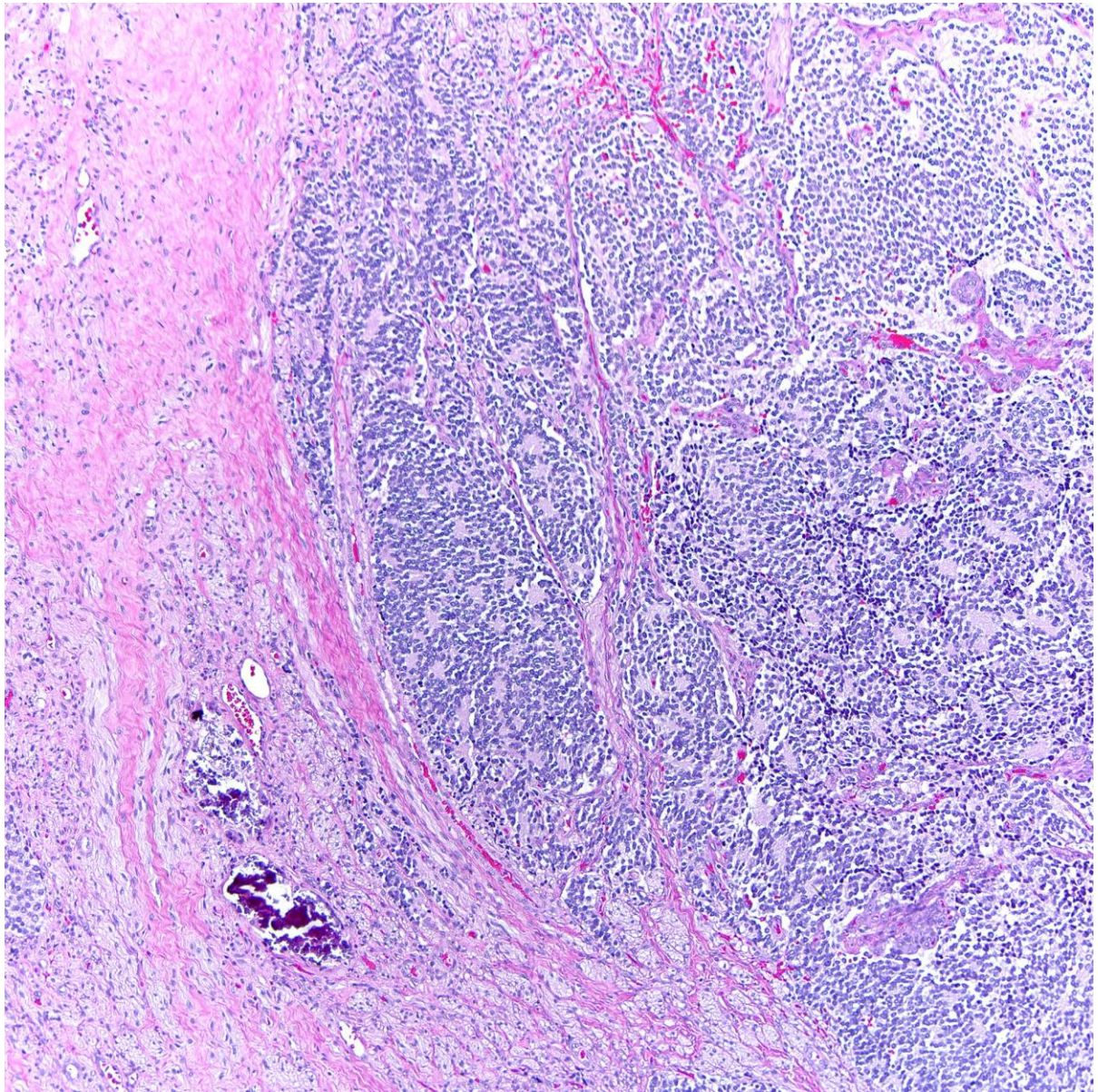
- GNBn shows macroscopic nodules formed by neuroblasts, surrounded by ganglioneuromatous elements.
- Nodular neuroblastic component with non-nodular Schwannian elements (stroma rich).
- Abrupt demarcation between the two components.
- Mitosis/karyorrhexis index (MKI) varies from low to high.
- The neuroblastic nodule determines whether it is of favorable or unfavorable histology. Each nodule should be analyzed independently for MKI in the context of age.
- Different areas may show *MYCN* amplification.
- Prognosis is generally unfavorable (60 to 83%).

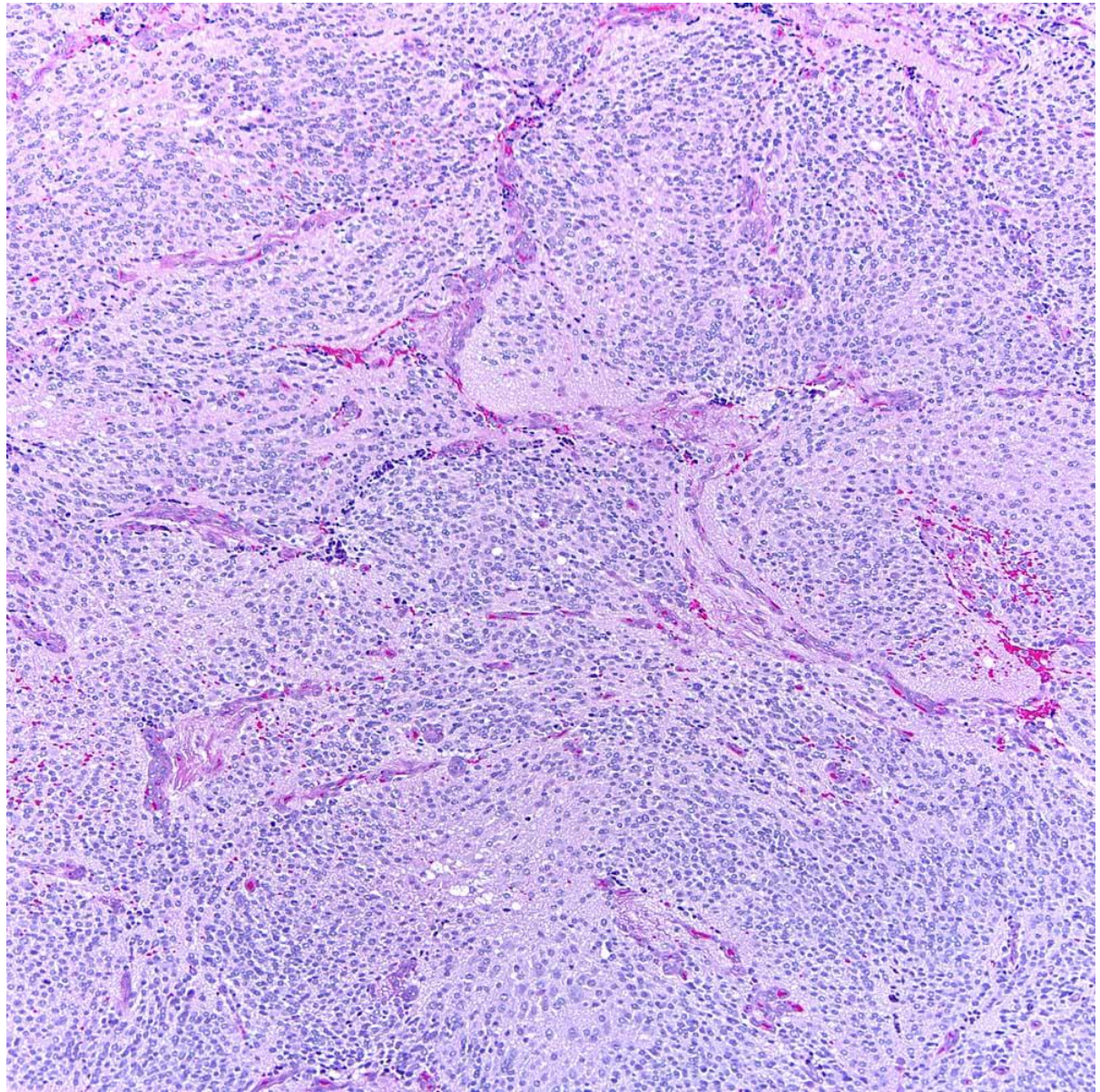
Ganglioneuroblastoma, nodular





Ganglioneuroblastoma, nodular





Neuroblastoma

- PNT derived from the neural crest, with <50% of Schwannian stroma.
- Subtypes:
  - Undifferentiated (3%): lymphoma appearance.
  - Poorly differentiated (89%): less than 5% of ganglion cell differentiation.
  - Differentiating (8%): 5-50% of ganglion cell differentiation.
- Adrenal (40%), abdominal extra-adrenal (25%), thoracic (15%), Cervical 3-5%. In 1% of patients the primary is not detectable.
- Variable symptoms depending on location and hormonal activity.
- Associated with Verner-Morrison sx. (diarrhea caused by VIP), Horner sx. (unil. ptosis, enopthalmos, myosis), opsoclonus-myoclonus-ataxia sx., hypertension.
- Ondine's curse and Hirschsprung disease (Haddad sx.) can be associated with neuroblastoma in cases of *PHOX2B* mutations.

Pediatric and Developmental Pathology 5, 190–199, 2002
DOI: 10.1007/s10024-001-0145-8

Hormonal Activity May Predict Aggressive Behavior in Neuroblastoma

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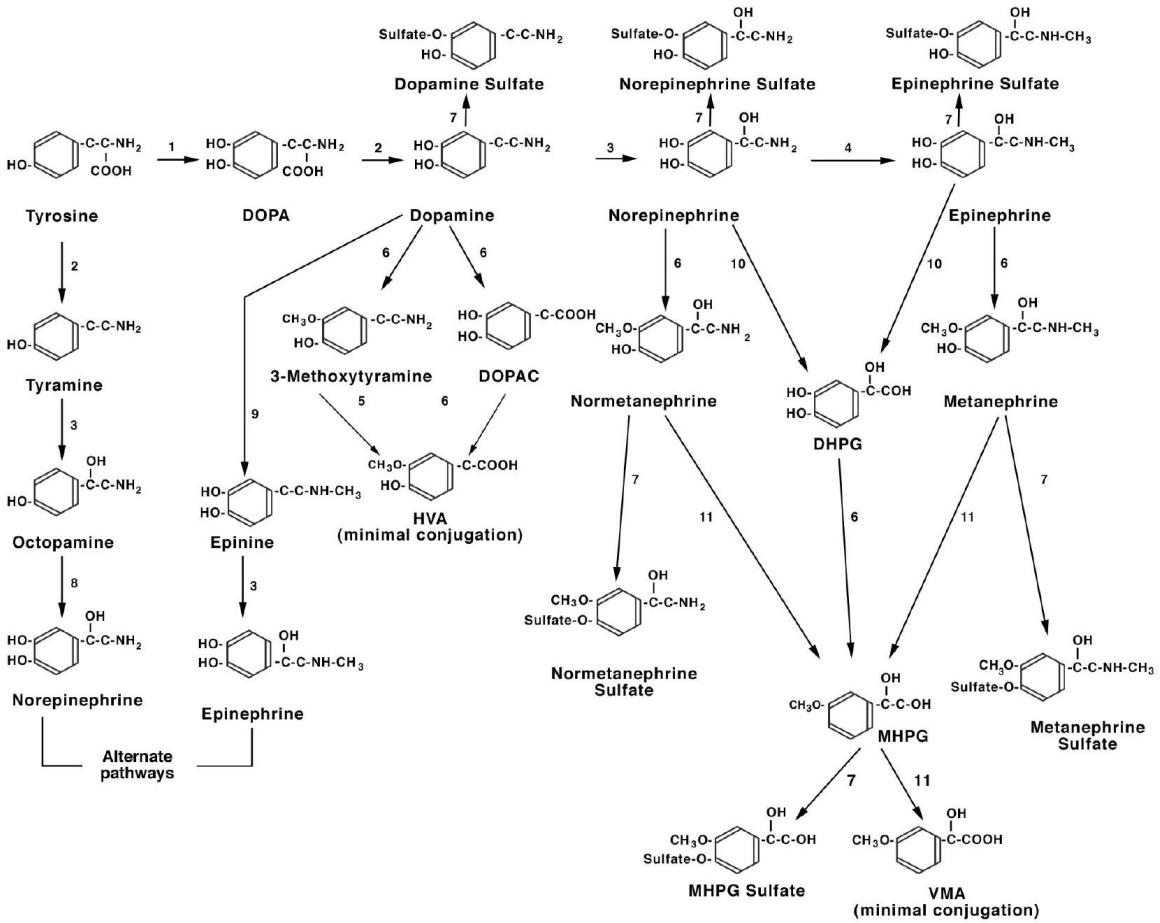


"…aggressive NB is associated with higher urinary levels of DA, VMA, HVA, and NE…"

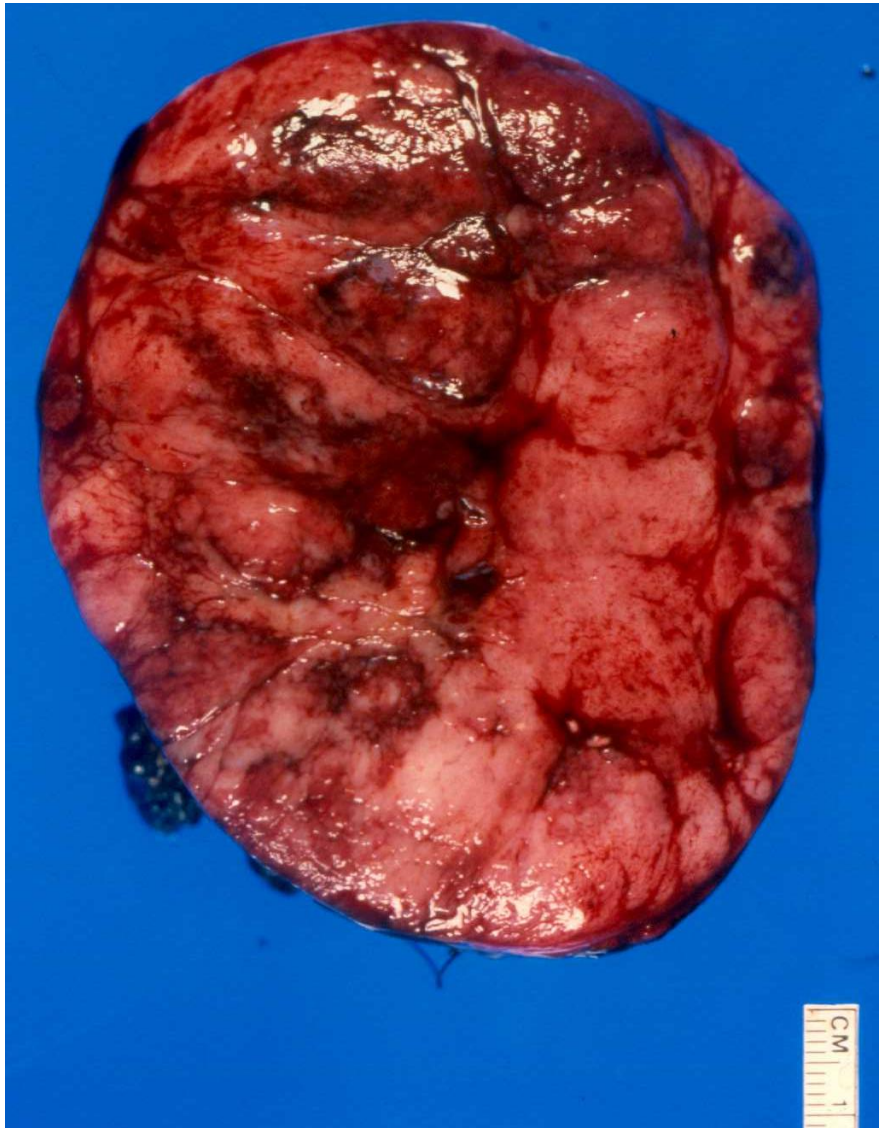
"…there appears to be a subset of NB in which a possible blockade in DA metabolism is associated with poor prognostic features (12 months, stage 4, UH, and MYCN amplification)…"

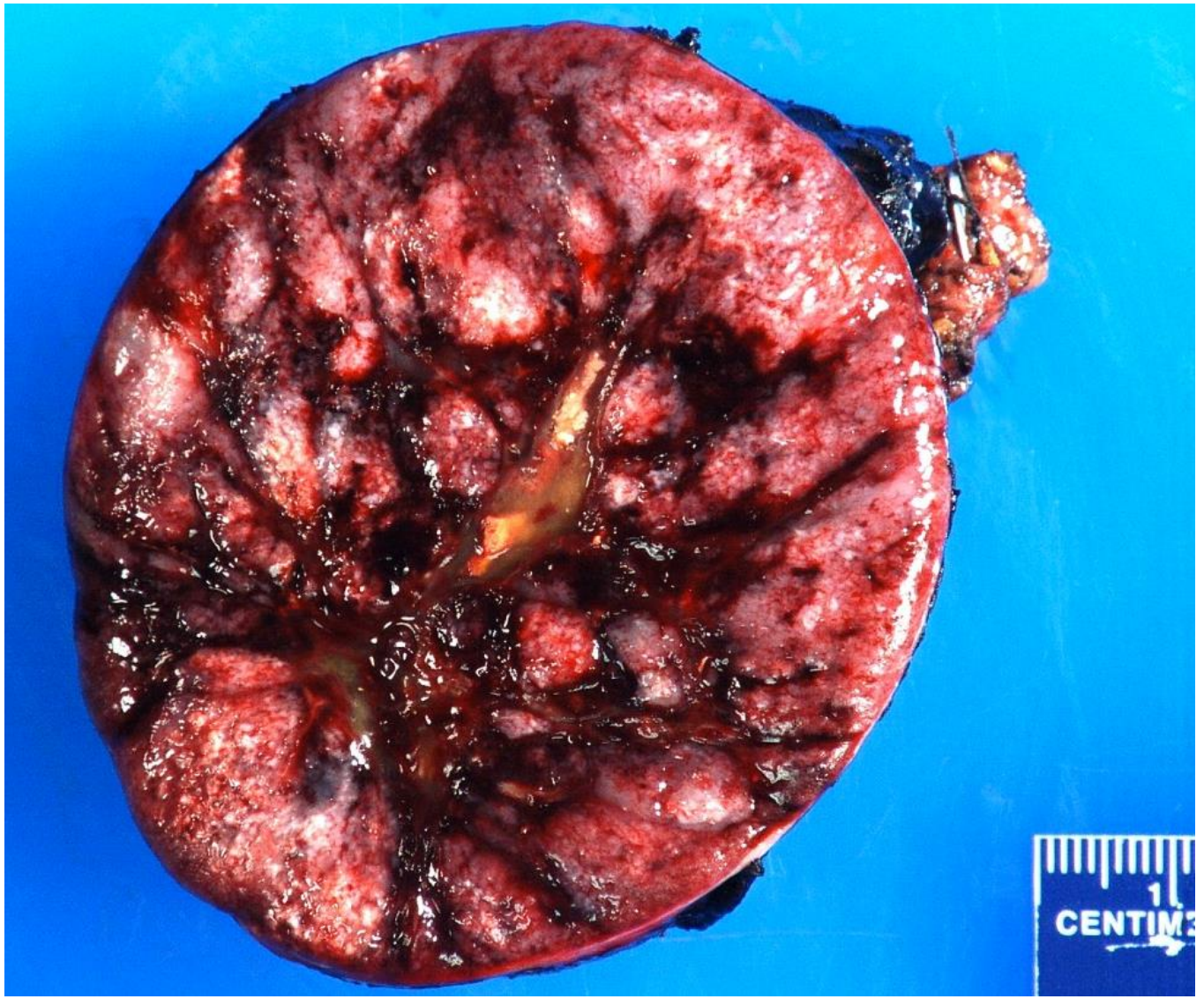
"A seemingly novel observation in our study is that all high DA/HVA and DA/VMA ratios were obtained in stage 4 tumors, suggesting an association between the inability to metabolize DA and the acquisition of metastatic potential."

"…we would like to emphasize the importance of determining not only DA, HVA, and VMA urinary levels, to support the diagnosis of NB, but also DA/HVA and DA/VMA ratios as a rapid initial assessment of prognosis in these patients."

@mreyesm

Neuroblastoma

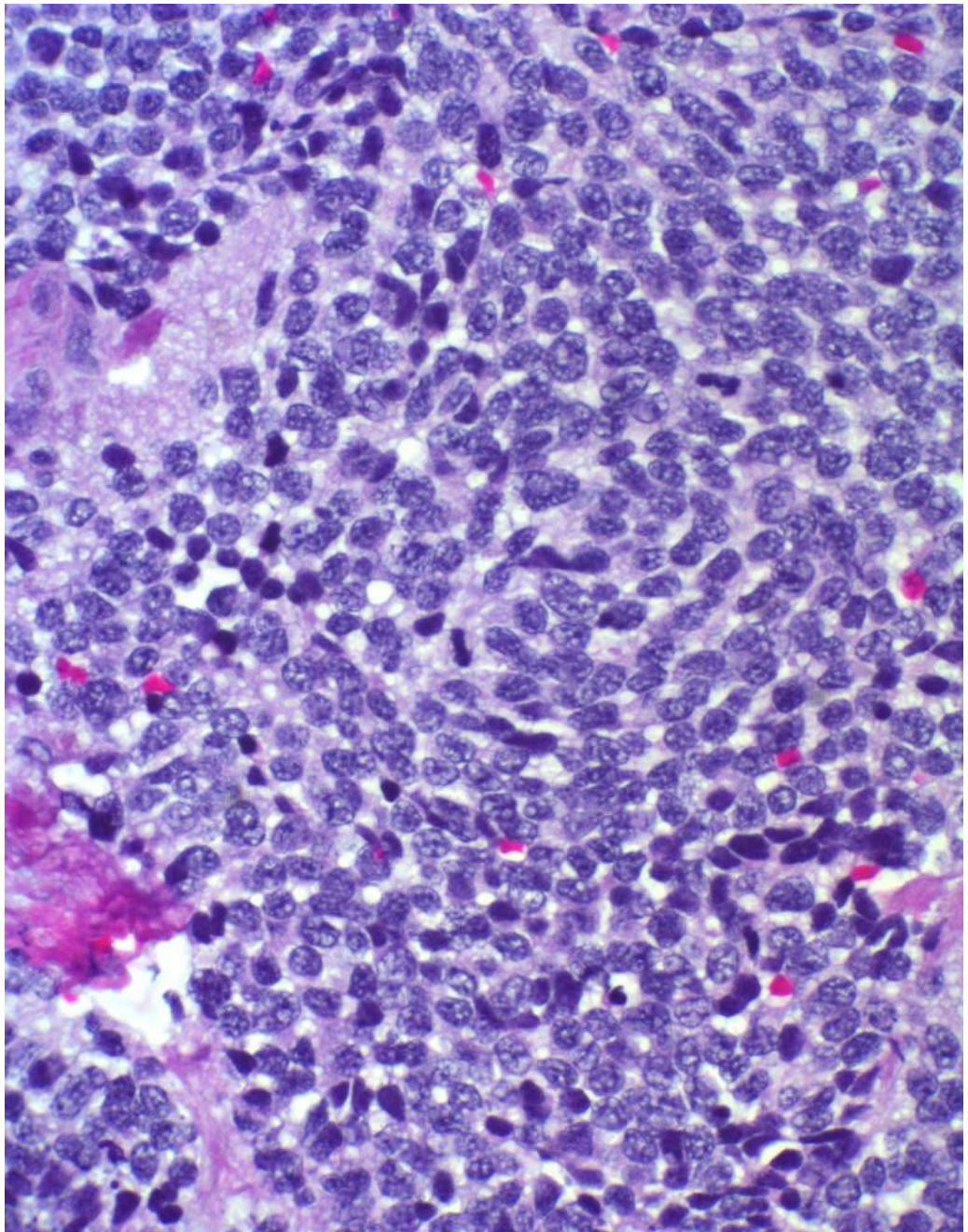


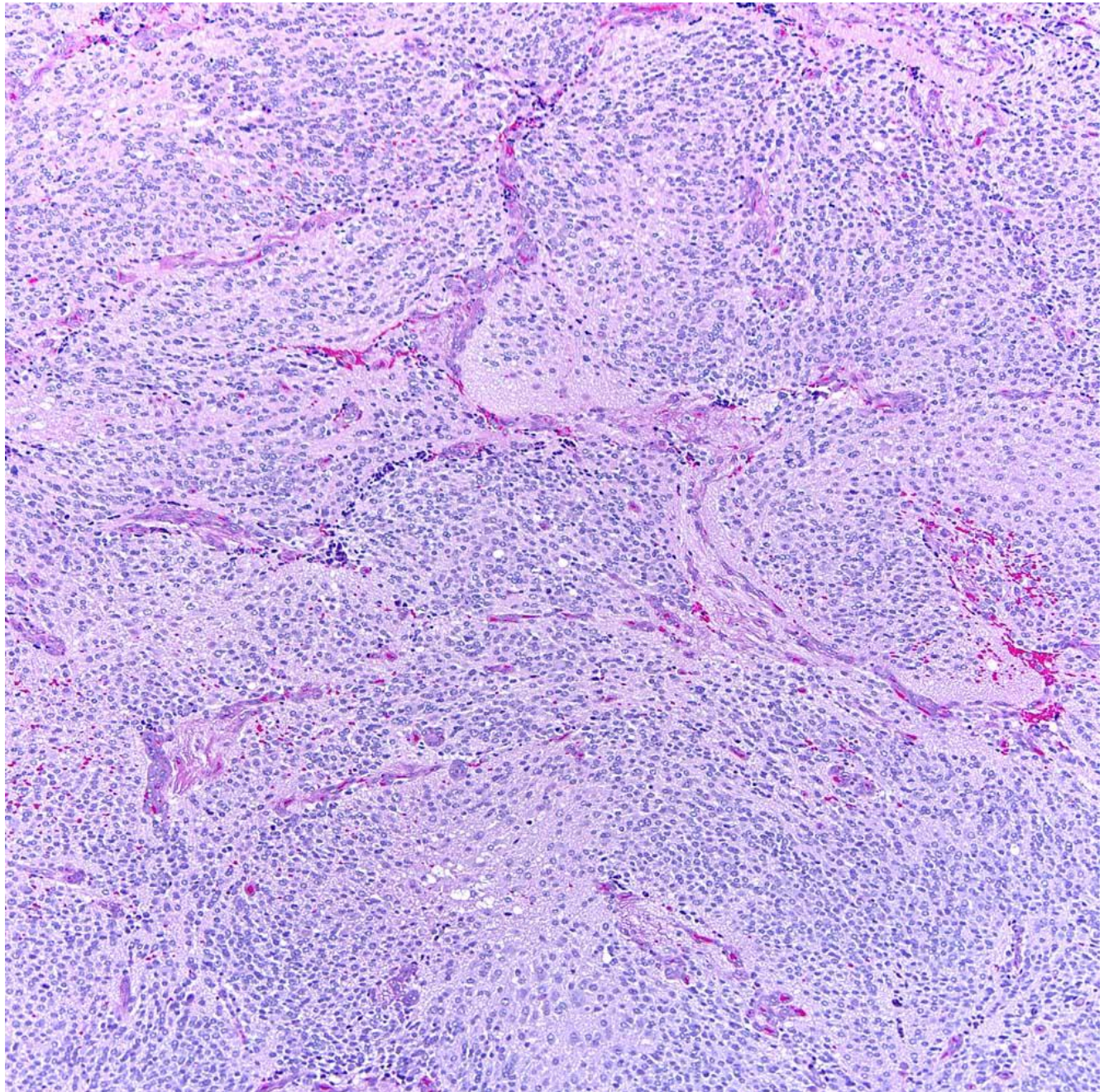


Neuroblastoma histology

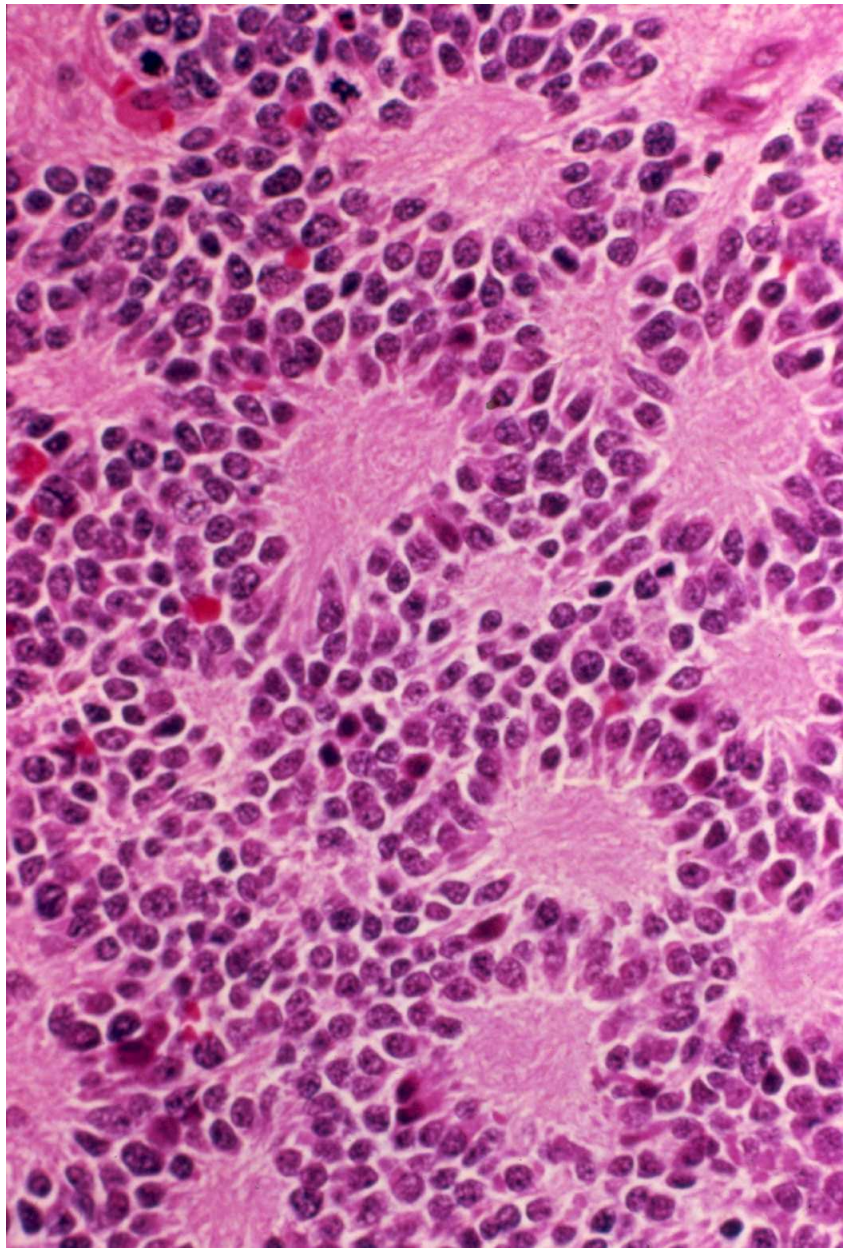
- The undifferentiated neuroblasts can look like lymphocytes, prototypical “small round ‘blue’ cell tumor”.
- As the differentiation progresses, features of immature ganglion cells appear.
- Neuropil and Homer Wright rosettes are classic findings.
- Nuclei have a “salt & pepper” appearance.
- Schwannian stroma is present is septa when there is a nodular arrangement. This can be highlighted by S-100 IHC.
- There are variable phenotypes, with large cells, pleomorphism, fusiform and pseudo-rhabdoid features. Large cell NBL is a highly aggressive subtype.
- Cytological analysis is NOT recommended due to heterogeneity.

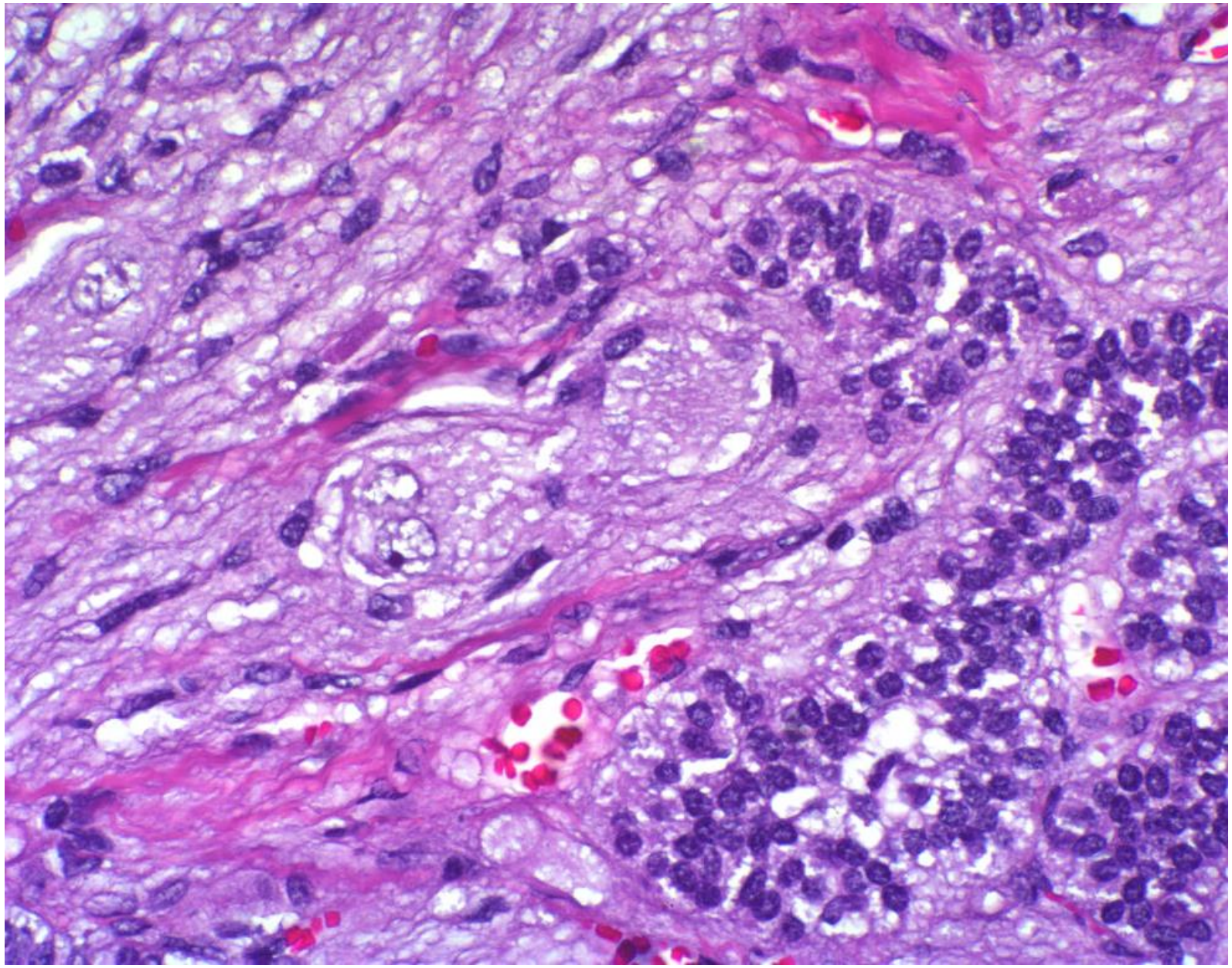
Neuroblastoma





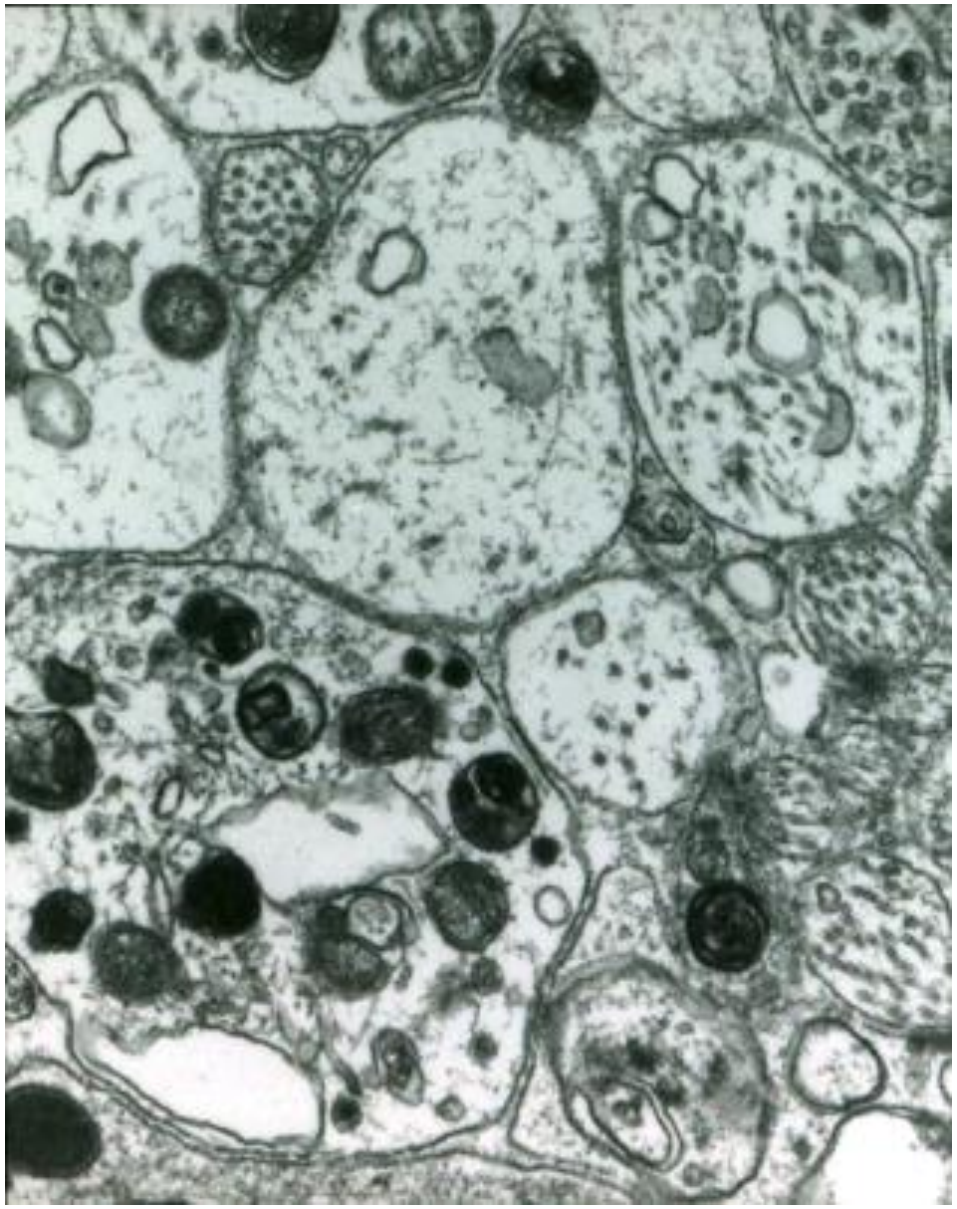
Neuroblastoma

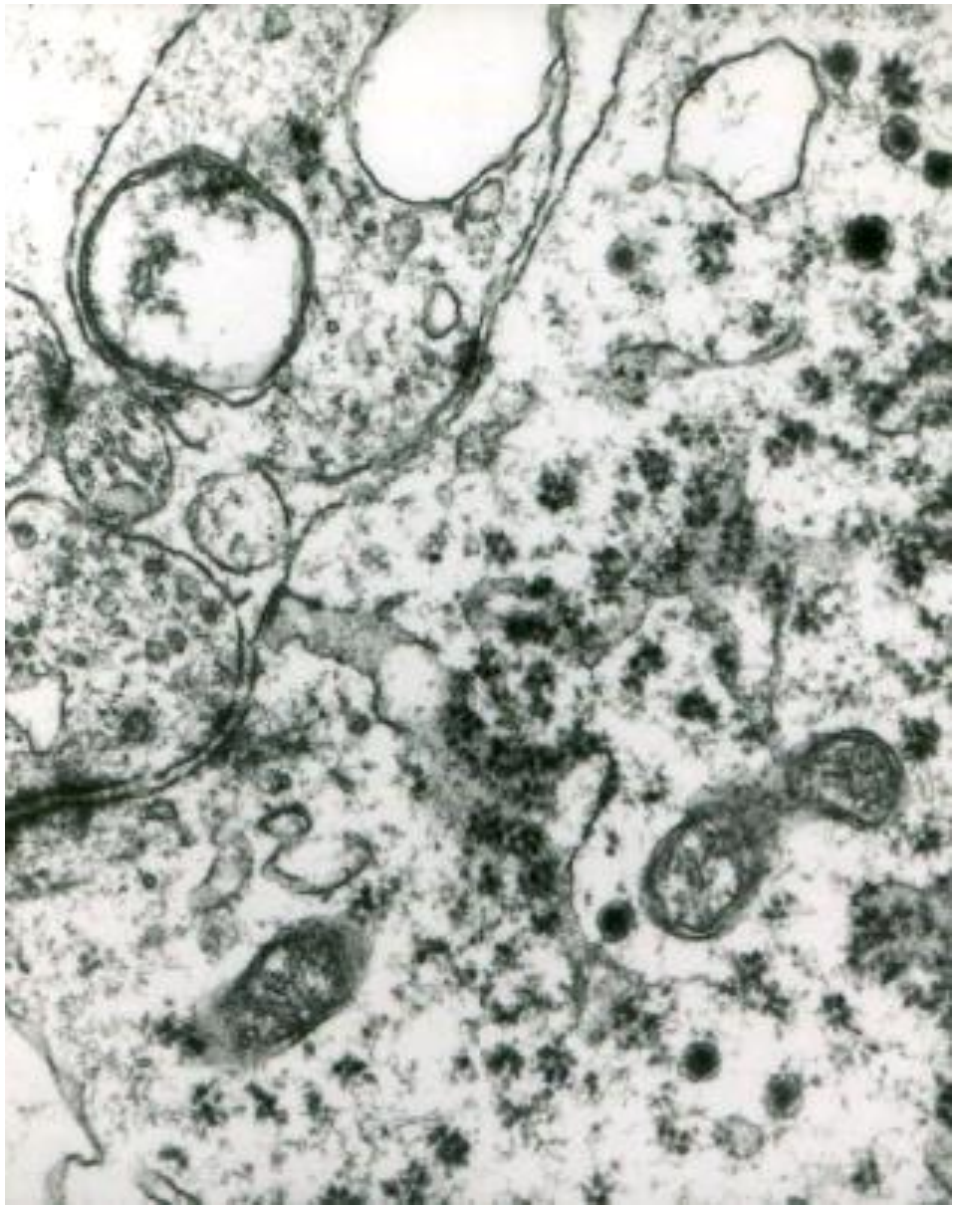




Homer Wright rosettes. Courtesy of J. Carrillo-Farga.

Neuroblastoma





Neuroblastoma, epidemiology

- PNTs: 3rd. most common malignant tumor of childhood, only surpassed by leukemias and brain tumors.
- PNTs: most common neoplasm in the first year of life.
- PNTs: most common solid tumors in the first 2 years of life outside of the brain.
- PNTs have a prevalence of 1 per 7,000 live births in the USA
- PNTs have a male:female=1.2:1 ratio
- Familial PNTs are rare, representing approximately 1-2%, most showing *ALK* (2p23) mutations, with incomplete penetrance (approx. 50%).

Neuroblastoma, etiology

- Genetic and epigenetic events lead to transformation of neural crest cells, causing neuroblastoma, but details remain poorly understood.
- Due to their onset in the very young, and based on the evidence of neuroblastoma *in situ,* these tumors are considered to start *in utero,* but more research is needed.
- Several important drivers in tumorigenesis for neuroblastoma include *MYC* and *ALK* overexpression, and a deficient telomere maintenance/elongation.
- Familial neuroblastoma occurs as an autosomal dominant disorder characterized by neuroblastic tumours that harbour constitutive activating germline mutations in the anaplastic lymphoma kinase gene (ALK), located on chromosome 2p23

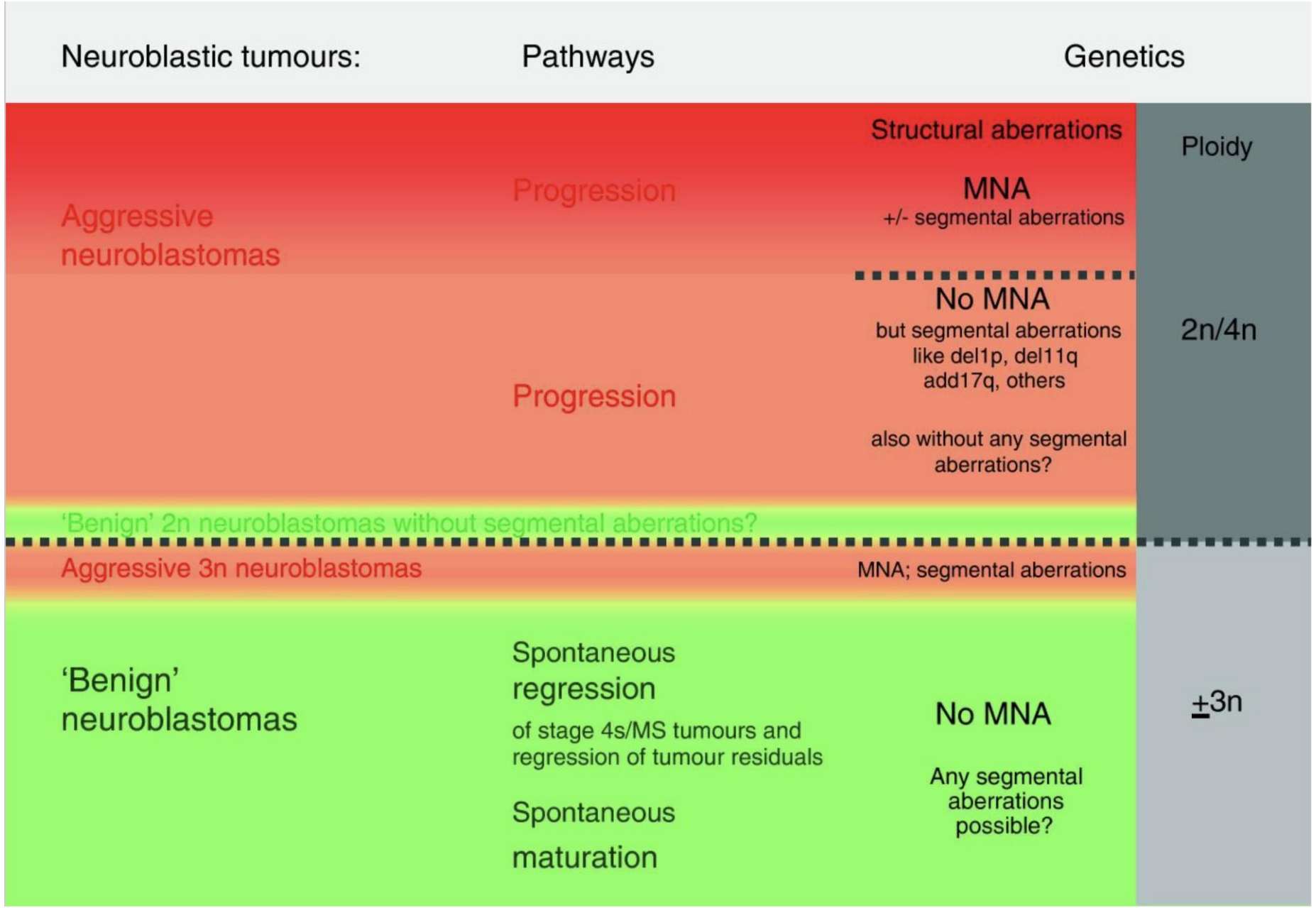
Neuroblastoma pathogenesis

- *MYCN* (2p24.3) is an important driver of NBL oncogenesis.
- Between 20 to 25% of NBLs show *MYCN* amplification (aka “MNA”).
- The *MYCN* locus appears as “double minute” chromosomes (DMs), or intrachromosomal homogenously staining regions (HSRs).
- FISH analysis establishes amplification of *MYCN* when the normal complement of 2 signals in chromosome 2 is increased fourfold or more.
- There are cases with gains (increased signals but less than fourfold), or non-amplified.
- Heterogenous intra-tumoral *MYCN* amplification is associated with an aggressive phenotype.

Neuroblastoma and *MYCN*

- *MYCN*-amplification is associated with advanced stage and aggressive behavior.
- *MYCN*-amplified tumors are of the undifferentiated or poorly differentiated subtypes, have a high MKI and fall into the unfavorable histology group (Shimada classification).
- Most (90%) *MYCN*-amplified NBLs overexpress MYCN protein.
- Rarely, NBLs show *MYCN*-amplification but no protein overexpression.
- Recently, MYCN protein overexpression (not MNA)has been recognized as the most important determinant of tumor aggressiveness.
- A few (~10%) NBLs overexpress MYC (aka C-myc) protein, but *MYC* amplification is extremely rare.
- NBLs with increased expression of either MYC or MYCN proteins (~20%) are very aggressive and frequently show prominent nucleoli, considered responsible for MYCN/MYC RNA synthesis and accumulation.
- Due to nucleolar hypertrophy, these MYC-driven NBLs also show “salt-and-pepper” nuclei, making them indistinguishable from common NBLs.

@mreyesm



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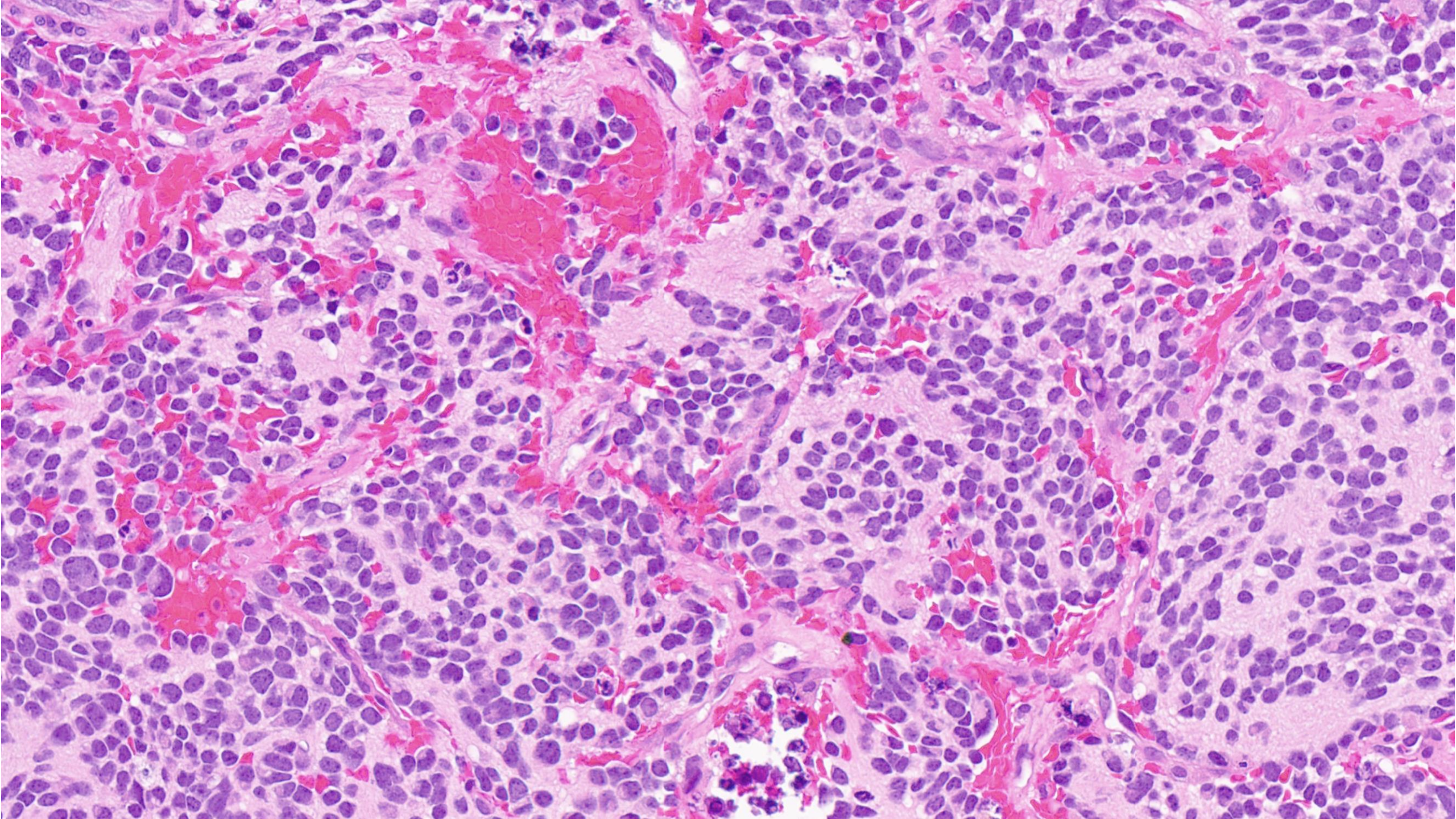

Relevant IHC in Neuroblastic Tumors of Children

- Synaptophysin
- Chromogranin
- Protein gene product 9.5
- CD56
- Neurofilaments
- Neuroblastoma marker (NB84)
- Neural crest markers:
  - Tyrosine hydroxylase
  - PHOX2B
- **PHOX2B: most reliable, even for undifferentiated subtype**
- Negative markers for other small round-cell tumours is recommended, especially in undifferentiated NBL
- S100 stains Schwannian stroma and Schwann cells precursors in fibrovascular septa

Other factors influencing NBL biology

- Telomere maintenance/elongation:
  - Telomerase
    - Adds short, repeated sequences at the end of chromosomes (telomeres)
    - Its expression is associated with cellular “immortality”
    - Up to 94% of neuroblastomas express telomerase; it is associated with *MYCN* amplification and bad prognosis
- *ALK* abnormalities (mutation, amplification), important in hereditary NBLs.
- 1p deletion, 11q deletion, 17q gain, are important in *MYCN*-non amplified NBLs
- Flow cytometry for DNA ploidy analysis:
  - Diploid and tetraploid tumors = poor prognosis
  - Hyperdiploid and particularly triploid tumors = favorable prognosis
  - Hypodiploid tumors = rare
- 6q loss associates with NBLs of extremely aggressive behavior.
- Many others: TRK-A, DCC, CD44, etc.

TABLE 41–1 Known Molecular Alterations in Pediatric Solid Tumors

Neoplasm	Gene	Locus/Translocation	Prognosis/Genetic Associations
Neuroblastoma	*MYCN*	2p23-24	Unfavorable, especially in stage 1 and 2
		1p36 LOH	Independent poor prognosis
		11q LOH	Independent poor prognosis
	DNA index	Hyperdiploidy (>1.0), near triploidy	Favorable in ages less than 1 yr old
	DNA index	Diploidy (1.0)	Early treatment failure in ages less than 1 yr old
		17q gain	Complex, related to other factors
	PHOX2B	4p12	Familial NB
	NBPF1	t(1;17)(p36.2;q11.2)	Familial NB

Picarsic, Nikiforova & Reyes-Múgica, 2012.

NBL subgrouping of unfavorable histology

- Unfavorable histology NBLs form a heterogeneous:
  - MYC subgroup (overexpressing MYCN or MYC protein).
  - TERT subgroup (TERT overexpression due to genomic abnormalities).
  - ALT subgroup (ALT phenotype due to ATRX loss).
  - Null subgroup.
- These can be determined by IHC for their protein markers which hopefully will allow targeted precision therapy

Prognostic categories
Int. Neuroblastoma Pathology Classification

Grade of Differentiation	Mitoses-Karyorrhesis Index	Age at diagnosis		
	MKI			
Undifferentiated (looks like lymphoma)	Any	0-18 Ms.	18 Ms-5 Ys.	> 5 years
Poorly Differentiated	Low: <100/5000 cells Intermediate: 100-200/5000 cells High: >200/5000 cells	Favorable Favorable Unfavorable	Unfavorable Unfavorable	Unfavorable Unfavorable
Differentiating	Low: <100/5000 cells Intermediate: 100-200/5000 cells High: >200/5000 cells	Favorable Favorable Unfavorable	Favorable Unfavorable Unfavorable	Unfavorable Unfavorable

Clinical types of neuroblastic tumors

Age	<1 year	>1 year	>1 year
DNA	Aneu/Trip	2N/4N	2N/4N
MYCN	No amplif.	No amplif.	>10
TRK-A	High	Variable	Low/neg.
1P-	Negative	Positive	Positive
Stage	1, 2, 4S	3, 4	3-4
Survival	95%	25-50%	5%

Spontaneous regression of neuroblastoma

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Spontaneous regression of neuroblastoma

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Abstract

Neuroblastomas are characterized by heterogeneous clinical behavior, from spontaneous regression or differentiation into a benign ganglioneuroma, to relentless progression despite aggressive, multimodality therapy. Indeed, neuroblastoma is unique among human cancers in terms of its propensity to undergo spontaneous regression. The strongest evidence for this comes from the mass screening studies conducted in Japan, North America and Europe and it is most evident in infants with stage 4S disease. This propensity is associated with a pattern of genomic change characterized by whole chromosome gains rather than segmental chromosome changes but the mechanism(s) underlying spontaneous regression are currently a matter of speculation. There is evidence to support several possible mechanisms of spontaneous regression in neuroblastomas: (1) neurotrophin deprivation, (2) loss of telomerase activity, (3) humoral or cellular immunity and (4) alterations in epigenetic regulation and possibly other mechanisms. It is likely that a better understanding of the mechanisms of spontaneous regression will help to identify targeted therapeutic approaches for these tumors. The most easily targeted mechanism is the delayed activation of developmentally programmed cell death regulated by the tropomyosin receptor kinase A (TrkA) pathway. Pan-Trk inhibitors are currently in clinical trials and so Trk inhibition might be used as the first line of therapy in infants with biologically favorable tumors that require treatment. Alternative approaches consist of breaking immune tolerance to tumor antigens but approaches to telomere shortening or epigenetic regulation are not easily druggable. The different mechanisms of spontaneous neuroblastoma regression are reviewed here, along with possible therapeutic approaches.

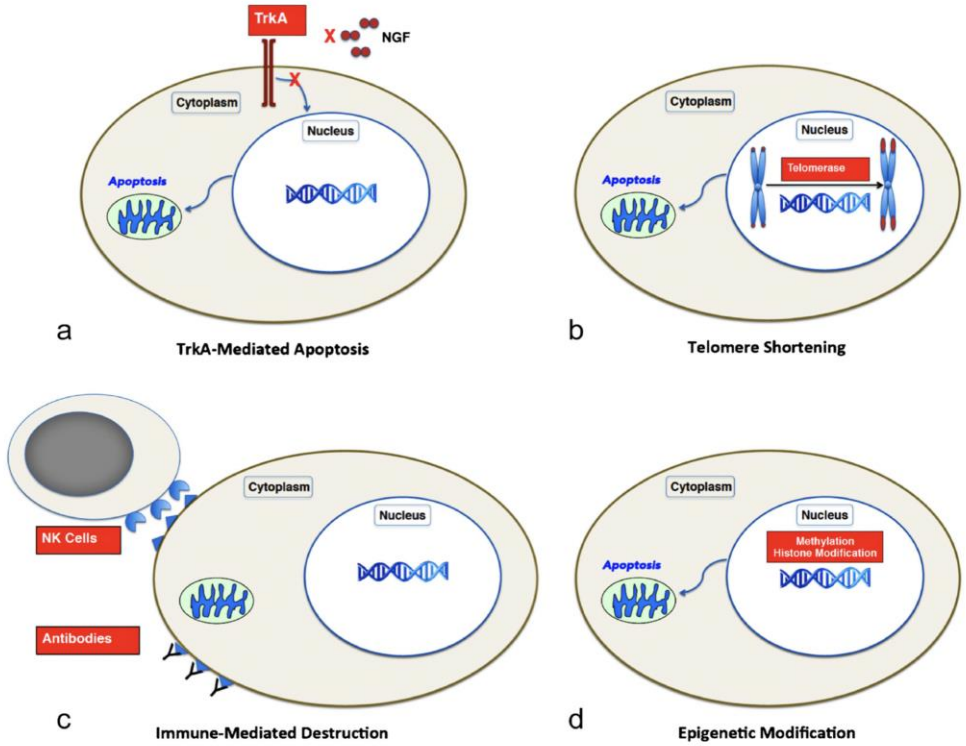

Fig. 1.
Mechanisms of spontaneous regression. **a** The TrkA-NGF pathway and apoptosis. Neurotrophin deprivation (TrkA without NGF) leads to activation of developmentally programmed apoptosis and regression of neuroblastomas. **b** Telomere shortening and apoptosis. Telomere shortening results from low/absent levels of telomerase and triggers apoptosis and regression of neuroblastomas. **c** Immune-mediated destruction. Immune-mediated cell killing by anti-neuroblastoma antibodies (and antibody-dependent cellular toxicity) or by NK cells leads to death of neuroblastoma cells and tumor regression. **d** Epigenetic modification. Alterations of gene expression can occur by promoter methylation, histone modification or chromatin remodeling, leading to neuroblastoma regression

@mreyesm

Kara Lombardo, Rita Alaggio, Cláudia M. Salgado, Martha Cohen, Hiro Shimada and Miguel Reyes-Múgica. LA, 2020.

Miguel Reyes-Múgica & Hiroyuki Shimada, LA, 2019